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DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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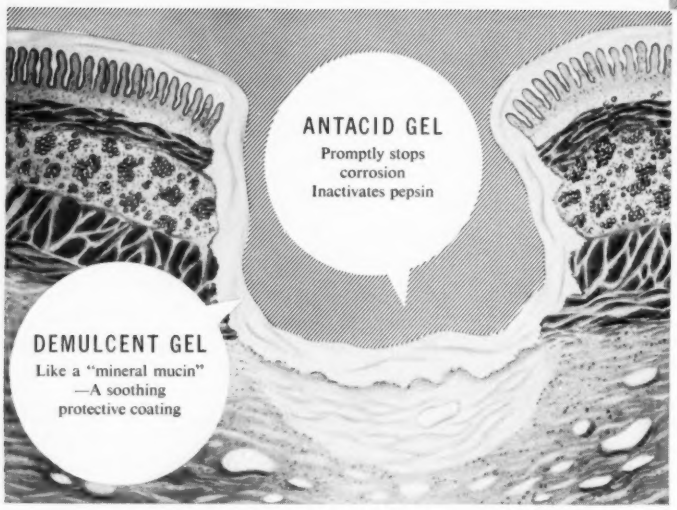

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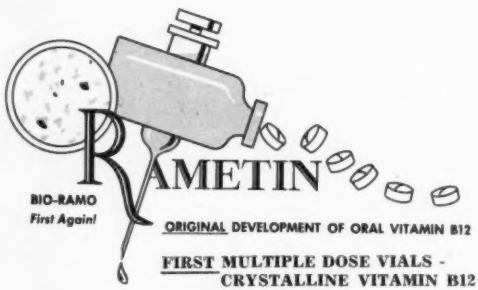

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Accruing clinical observations clearly indicate that a diet high in complete protein and in the B complex vitamins is a highly successful measure in management of cirrhosis of the liver. Connor states that, prophylactically, a well nourished individual on a diet optimal in protein content and other essentials does not develop cirrhosis.[1]

A recent study[2] again substantiates the finding that proper dietary control improves the prognosis in hepatic cirrhosis. In this study the results from the dietary treatment of 124 patients with cirrhosis of the liver in failure were compared with the results from a control group of 386 patients with hepatic cirrhosis. The severity of the underlying disease process was comparable in both groups.

The dietary regimen of the test group included generous amounts of protein supplemented with vitamin B concentrates; bed rest, diuretics, abstinence from alcohol, and supportive care were also prescribed. Providing about 3,500 calories, the diet contained 140 Gm. of protein, 365 Gm. of carbohydrate, and 175 Gm. of fat. It consisted largely of meat, milk, eggs, fruit, and green vegetables. Yeast or a vitamin B complex preparation was also administered. Thiamine (5 mg., daily) and unconcentrated liver extract (5 cc., twice weekly) were injected intramuscularly. On the other hand, the control group received bed rest, supportive care, and diuretics but no specific dietary measures other than a diet high in carbohydrate and low in protein and fat.

As indicated by the statistical results, it was concluded from this study that Laennec's cirrhosis is not necessarily a progressive disease. After several months of treatment clinical improvement was observed in 61 of the 145 patients. Duration of life after onset of ascites was significantly greater than in the control group. At the end of one year, 65 per cent of the treated patients were alive against only 39 per cent of the controls; at the end of two years, 50 per cent of the treated patients and 21 per cent of the controls were alive; and at the end of five years 30 per cent of the treated patients and only 7 per cent of the controls survived. Early diagnosis and treatment, however, should improve the prognosis indicated by these findings.

The value of meat in the dietary control of hepatic cirrhosis is not limited to just its high content of biologically complete protein. Meat also provides valuable amounts of the B vitamins—riboflavin, thiamine, niacin, and the recently discovered vitamin B_{12}.

---

1. Connor, C. L.: The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver, J.A.M.A. 112:387 (Feb. 4) 1939.

2. Patek, A. J., Jr.; Post, J.; Ratnoff, O. D.; Mankin, H., and Hillman, R. W.: Dietary Treatment of Cirrhosis of the Liver, J.A.M.A. 138:543 (Oct. 23) 1948.

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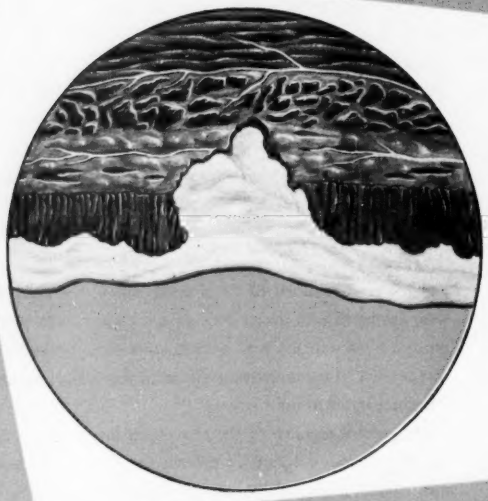

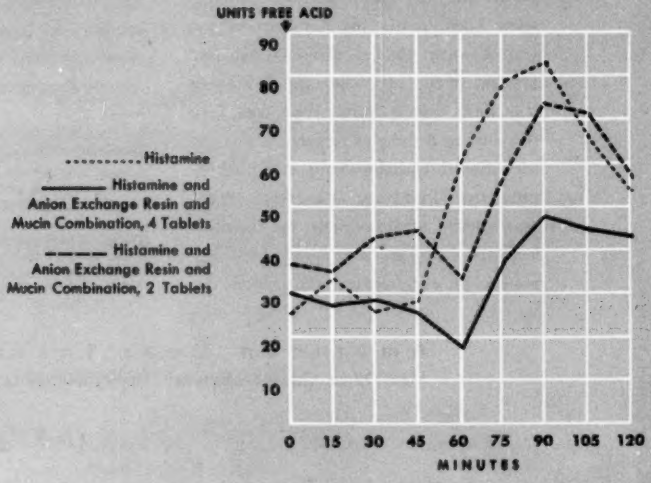

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*Steigmann, F., and Schlesinger, R. B.: A Resin-Gastric Mucin Mixture in the Medical Management of Peptic Ulcer, American J. Dig. Dis. *17*:361-365 (Nov.) 1950.

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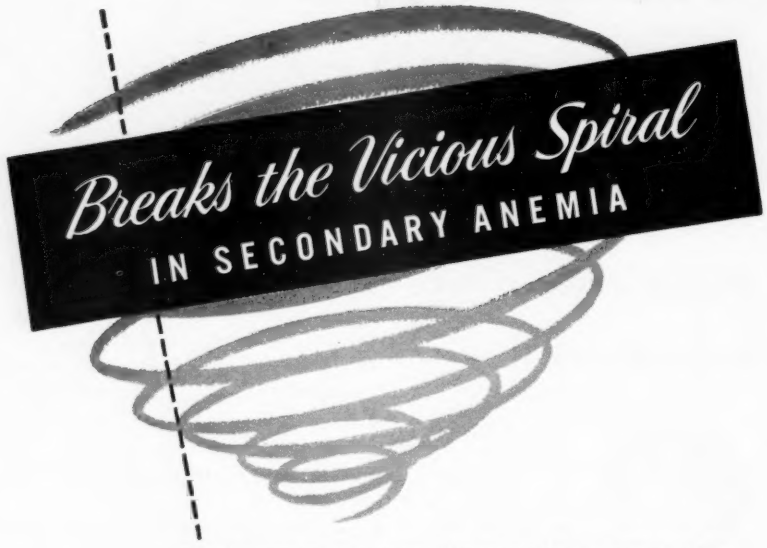

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INFECTION OF THE GALL BLADDER AND DIABETES

HENRY J. JOHN, M.D., Cleveland, Ohio

FOR THE PAST FIFTY YEARS, investigators have observed and explored the relationship between diabetes and disease of the gall bladder. The intimate anatomic and functional relationships of the gall bladder with the liver and the pancreas have been extensively studied, and yet numerous questions and disagreements remain as to the mechanism of the changes observed and the final results of such changes. Since the regulation of carbohydrate metabolism is centered to such a large extent in the liver and pancreas, any infection of the gall bladder which distorts or disrupts the function of these organs is certain to produce temporary changes in the ability of the body to utilize and store sugar, which may become permanent and irreversible, resulting in clinical diabetes. In view of the uncertainties and questions that still exist in connection with this problem, it seems worth while to review my own findings in a series of cases that I have observed over a prolonged period, along with salient clinical and experimental investigations bearing on this problem which have been reported in the medical literature.

CLINICAL OBSERVATIONS IN THE LITERATURE

The fact that drainage or removal of an infected gall bladder in a diabetic patient results so often in great improvement or even disappearance of diabetes has been cited frequently in the literature. This is not surprising in view of the fact that cholecystitis is a frequent cause of pancreatitis, and pancreatitis is quite generally accepted as the common cause of diabetes (Allen, 1, 2).

Lancereaux (3), in 1899, was the first one who called attention to the intimate relationship between an infected gall bladder and pancreatitis and, inferentially, diabetes mellitus. Mayo-Robson (4) and Murphy (5) showed that in patients with cholecystitis and glycosuria they could effect a permanent disappearance of the glycosuria by drainage of the infected gall bladder.

In 1914, W. J. Mayo (6) stated that chronic pancreatitis is extremely common in cholecystitis and advised the surgical treatment of the gall bladder for the cure of it. Deaver (7) asserted that the most frequent forerunner of disease of the pancreas is some infection of the gall bladder or the bile passages, which is often, but not always, associated with calculi. Sweet (8) advanced the proposition "to continue to think of chronic pancreatitis as lymphangitis, secondary to a focus infection in the wall of the gall bladder, and I shall continue to remove the focus of infection and cure the condition."

Eustis (9), in 1923, expressed the belief that infection of the gall bladder and of the common duct extends to the pancreas and causes inflammatory changes which may eventually lead to the development of diabetes. In the same year, Rabinovitch (10) made a study of the blood sugar in patients in the Montreal General Hospital who presented symptoms of cholelithiasis and found that in more than 80 per cent hyperglycemia was present.

Harris (11) stated that "a pancreatitis is often secondary to gall bladder disease and that a preceding pancreatitis, from which results permanent damage to the islands of Langerhans that secrete the hormone, now called insulin, is usually the direct or predisposing cause of diabetes." Allen (12), in discussing Harris's paper, stated that surgical removal of infected foci, including the infected gall bladder, is desirable for either prophylaxis or treatment of diabetes, indicating that an etiologic relationship between an infected gall bladder and diabetes does exist. Barling (13) expressed the belief that the dominant factor in practically all cases of pancreatitis is the infection from the biliary passages. If this is true, then the infection of the biliary passages is also responsible for the development of diabetes, since, according to Heiberg (14), "when a chronic pancreatitis is present, diabetes will make its appearance sooner or later." Heyd and Killian (15) stated that "many cases of gall bladder disease show a definite increase in blood sugar. In fact, a blood sugar as high as 200 mg. per cent is not uncommon. However, following adequate surgical therapy for the disease of gall bladder or biliary ducts, the blood sugar readjusts itself to normal." In 1924, Lichty and Woods (16), in discussing the significance of glycosuria in disease of the gall bladder and ducts expressed their conviction that the frequent association of gall bladder disease with diabetes is not merely a matter of chance, but that the two stand in causal relationship. They reported three instances in which the patients were apparently cured of diabetes as a result of operation upon the biliary tract. After studying the pancreatic and hepatic activities in diabetes mellitus, Jones (17) arrived at the conclusion that "in adults cholecystitis is probably one of the most important etiologic factors in diabetes mellitus."

The foregoing early observations on the relationship of cholecystitis to diabetes mellitus have been corroborated and extended by numerous investigators during recent years.

Bohan (18) emphasized the importance of the postprandial blood sugar in the diagnosis of decreased carbohydrate tolerance in disease of the gall bladder. In his opinion, such a decrease of the carbohydrate tolerance may not be a true insular one, but may be due to disturbance of liver function caused by the toxic effects of the cholecystic disease, resulting in the derangement of the homeostatic control of the blood sugar. To improve the liver function, he advocated a high carbohydrate, high protein diet, reduction of weight if obesity is present, and perhaps removal of the affected gall bladder.

Pavel (19) called attention to the pancreatitis which occurs frequently as an accompaniment of certain infections, especially mumps, which is often followed by hyperglycemia and diabetes. After pneumonia and catarrhal jaundice, according to Pavel, the damage to the pancreas is reversible.

Submitted Sept. 11, 1950.

In his studies of the sugar metabolism in epidemic hepatitis, Urech (20) found abnormalities of the blood sugar in the glucose tolerance tests. He noted the appearance of temporary diabetes in children so affected and its subsidence with improvement in the hepatic condition; conversely, in adults permanent diabetes with a poor prognosis often developed.

Mosenthal (21) called attention to gall stones and inflammation of the gall bladder as causing pancreatitis and consequently, diabetes. An ascending infection through the bile ducts with consequent liver involvement is a much more frequent cause of diabetes. Pavel and Florian (22) reported that in 1,000 cases of diabetes mellitus, a history of gall bladder disease was present in 289, or 28.9 per cent.

The frequent association of diabetes mellitus with cirrhosis of the liver was noted by Bohan (23). He explained this by the fact that the homeostatic control of the blood sugar is disturbed and also that protein metabolism is severely affected. Certain amino acids cannot be formed in the body; hence a nutritional defect in these essential factors, i. e., histidine and proline, may interfere with the secretion and action of insulin.

Leevy, Ryan and Fineberg (24) performed various hepatic tests on 380 diabetic patients to determine the incidence of liver dysfunction and its relationship to the etiology of manifest hyperglycemia with glycosuria. Of the cases studied, 38.9 per cent were found to have liver dysfunction. Of 130 patients with complications, 55.3 per cent had hepatic dysfunction. Of those without evident complications, the incidence of abnormal hepatic function was 30.4 per cent. These authors stated: "Sixty-five patients with the diabetic syndrome and evidence of hepatic dysfunction have been followed up for periods of more than twelve months on a hepatic regimen. Correlation of history, physical examination, function studies and therapeutic response suggest hepatic dysfunction was responsible for abnormal carbohydrate metabolism in fifteen patients, liver dysfunction was secondary to diabetes in forty-eight patients, and liver disease and diabetes were coincidental in two patients. One patient had diabetes and hepatic dysfunction which were attributed to obesity." They added further: "Liver dysfunction may occasionally produce the diabetic syndrome or be secondary to it. In eleven patients in whom hepatic disease was believed to be the cause of hyperglycemia with glycosuria, hepatic therapy without insulin resulted in improvement in the hepatic dysfunction and carbohydrate disturbance. Of thirty-five clinic patients with liver dysfunction secondary to diabetes, the hepatic abnormality and carbohydrate tolerance improved with hepatic therapy and insulin in thirty."

Portis (25) noted a form of liver disease not commonly recognized which he called "cholecystohepatohyperglycemia and glycosuria syndrome." Patients with this condition usually present a long history of gall bladder disease interspersed in most instances with attacks of acute or subacute suppurative cholecystitis, usually with non-visualization of the gall bladder. Portis contended that the sugar tolerance in these cases is not that of true diabetes but more like that of liver disease. He offered objections to the giving of insulin for the control of the hyperglycemia, no matter how high the level of the blood sugar. He explained the hyperglycemia as follows: Glycogenolysis is more rapid than glycogenesis and the insulin further depletes the storage of glycogen by the liver and hence increases the glycogenolytic process still further. Thus the liver is further damaged when its protective mechanism of glycogen reserve is lowered. He advocated dextrose administered intravenously to prevent the rapid glycogenolytic manifestation and to reverse the process, thus enabling the liver to store more glycogen. His observation was that by this procedure the fasting blood sugar was lowered with disappearance of glycosuria and "no evidence of diabetes" remained, other than the elevated level of blood sugar. (According to this interpretation, a lasting hyperglycemia is not regarded as evidence of the presence of diabetes.)

Taub and his associates (26) pointed out that there are numerous conditions other than diabetes mellitus which are accompanied by hyperglycemia, such as obesity, liver damage and hyperpituitarism. The concentration of the sugar in the blood is determined not only by the level of insulin, but also by the state of the liver, kidneys and the gastro-intestinal tract as well as by the level of the pituitary-adrenal hormones. A majority of adult "insulin-sensitive" diabetics do not have true diabetes, according to these authors, but are suffering from injury to the liver and one of the indications of their hepatic dysfunction is hyperglycemia. Liver damage does not affect the glycogen balance to cause an overproduction. Indeed, if the damage is severe, the reverse may be true. Insulin plays no part in the therapy of cases of this type and may cause harm if its administration is continuous. They advocated giving 400 to 800 grams of carbohydrate, which has a restorative action upon the liver parenchyma and thus reduces the work of the liver in supplying carbohydrate lost in the urine.

EXPERIMENTAL STUDIES IN THE LITERATURE

In 1926, Ricen (27) published experimental work on cholecystitis and diabetes. His work was done on two groups of dogs, one in which the gall bladders were intact and one in which the gall bladders had been removed. He stated: "My object was to produce an experimental cholecystitis . . . by repeated infections to perpetuate the inflamed condition of the gall bladder, hoping to produce thereby a chronic pancreatitis. I expected to find evidence of damage to the islands of Langerhans with consequent diabetes symptoms, if the pancreatitis is kept up for a sufficiently long period. The cholecystectomized (second) group of dogs, was to be subjected to the same process of reinfection as the first group, with the object to ascertain whether the absence of the gall bladder would make any difference in the causation of diabetic symptoms."

He demonstrated in the dogs with gall bladders intact that lesions of the islands of Langerhans, resulting in diabetic symptoms, could be caused by injections of streptococcus hemolyticus and bacillus typhosus, if these were carried out over a sufficiently long period. The microorganisms injected which produced fever could be isolated from the gall bladder and after a series of injections, a definite diabetic curve of the blood sugar was observed. At autopsy

there was evidence of inflammation in the sections of the gall bladder, liver and pancreas, as well as toxic damage to the islands of Langerhans. In the dogs whose gall bladders were removed before the experiment and who went through the same series of injections with the bacteria, there was no evidence of damage to the islands of Langerhans as judged by the glucose tolerance tests. Ricen emphasized: "The fact that we never succeeded in lowering the sugar tolerance in animals with their gall bladders removed would seem to point to the importance of the infected gall bladder in damaging the pancreas and particularly the islands of Langerhans, to such an extent as to produce diabetic symptoms."

Hepatic Glycogen in Obstructive Jaundice. Abundance of hepatic glycogen furnishes the basis for the protective and regenerative action of high carbohydrate diets in liver necrosis in experimental cirrhosis of the liver and in obstructive jaundice. There are two methods of administering dextrose, by mouth and intravenously. Althausen (28) pointed out that in an individual weighing 70 kilograms (154 pounds) a daily minimum of 560 grams of carbohydrate is theoretically required to insure adequate deposition of glycogen in the liver. When the amount of glycogen in the liver is adequate, the RQ approaches unity, allowing a sparing of fat and protein and a proper utilization of carbohydrate for the production of the energy requirements of the organism. If the patient cannot take such an adequate amount of carbohydrate by mouth, owing to anorexia, nausea, vomiting or diarrhea, caused by obstructive or intrahepatic jaundice, then the carbohydrate has to be supplied intravenously in order to prevent the depletion of glycogen in the liver.

To ascertain whether the oral or the intravenous administration of glucose is more effective, Banks and Sears (29) made an investigation on fifty-five dogs, male and female. Their results (Table I) showed that dextrose was more efficacious by vein than by mouth in raising the glycogen content of the liver in dogs with obstructive jaundice. This method permitted the prompt introduction of larger amounts of sugar and water than is usually possible by oral administration. This increased the hepatic glycogen and also replenished the wants of the heart and skeletal muscle.

TABLE I

HEPATIC GLYCOGEN IN OBSTRUCTIVE JAUNDICE
Banks and Sears (29)

Jaundiced dogs on standard diet	*Daily ration of supplementary dextrose*	*Method of dextrose administration*	*Hepatic glycogen per kg. of weight*	*Ratio of liver weight to total weight*
Controls 6 dogs	none	———	0.196	0.316
Group I 12 dogs	75 grams	oral	0.227	0.343
		intravenous	0.751	0.370
Group II 18 dogs	100 grams	oral	0.673	0.351
		intravenous	0.760	0.406

Markowitz (30) pointed out that glycogen is an obligatory and not an optional step in the formation of blood sugar from the non-carbohydrate stores of the organism. The sugar hunger resulting from impaired gluconeogenesis is reflected throughout the organism; for example, the heart may require treatment even though the glycogen in the liver is not depleted.

Evans (31) found that cardiac glycogen may be increased by the use of glucose but that it is not further increased by the use of insulin. In animals receiving injections of glucose the liver glycogen was lowered by the use of insulin in proportion to the size of the dosage. This effect occurred even during hyperglycemia.

Usually the liver glycogen is decreased in the following conditions: (1) when the antitoxic activity of the liver is decreased by bacteria or toxins; (2) when oxidation of fats is decreased; (3) when oxidation of ketone bodies is decreased (acetoacetic and oxybutyric acids); (4) when oxidation of amino acids is decreased (Abderhalden); (5) in glycosuria of the pregnant woman which may end in a sudden coma; (6) in cases of icterus, resulting from the administration of arsenical medication, and (7) when the toxicity of the urine is increased.

MECHANISM OF LIVER FUNCTION IN CARBOHYDRATE METABOLISM

The liver is one of the organs which functions earliest in fetal life, when it is principally a blood-forming organ. After birth and later in life it becomes an instrument involved in the regulation of metabolic changes, of water balance and of the circulation of the blood. As the result of its secretion of bile, the liver aids in the assimilation of food in the intestines. The bile excreted by the liver contains many unused substances from the blood, some of which arise as the result of the chemical changes involved in metabolism and others which are noxious or waste materials that have been ingested. The liver also assists in the storage and promotion of various activities of the vitamins and the hormones. Although all its activities are still not thoroughly and completely understood, there is no question that the liver is a primary vital organ of the human body.

The effect of the liver on the carbohydrates is well known. The monosaccharides (glucose, fructose, galactose and mannose), the disaccharides (saccharose, lactose and maltose) and the polysaccharides (starch and cellulose) are broken down through the aid of the fermentive processes in the digestive apparatus, and are transported to the liver by the blood stream through the portal vein. Most of the carbohydrates are retained by the liver but a portion flows over into the general circulation, causing a rise of blood sugar, the so-called alimentary hyperglycemia. This elevation of sugar begins to subside in about an hour and by the end of two hours, reaches the normal level. The tissues, especially the muscles and the liver, absorb much of the circulating sugar which is partly oxidized and partly deposited as glycogen. For this reason, the arterial blood sugar is somewhat higher than the venous.

The activity of the liver is controlled by the vagus and the sympathetic nerves. It has no automatic ganglia of its own. Besides the nervous control, the various hormones exert a chemical regulatory function.

When there is a derangement of liver function, the hyperglycemia present after eating reaches higher levels and is more prolonged than normal owing to the insufficiency of the liver cells in performing their function in the carbohydrate metabolism. When jaundice is present, there are concomitant changes in the liver, with degeneration of liver cells, i. e., hepatitis of some type. A clinical connection between parenchymal icterus and Laennec's cirrhosis is certain, according to Pelnář (32). For this reason, the question whether such embarrassment of the liver, leading to abnormal hyperglycemia, can cause permanent diabetes, is pertinent and of clinical importance.

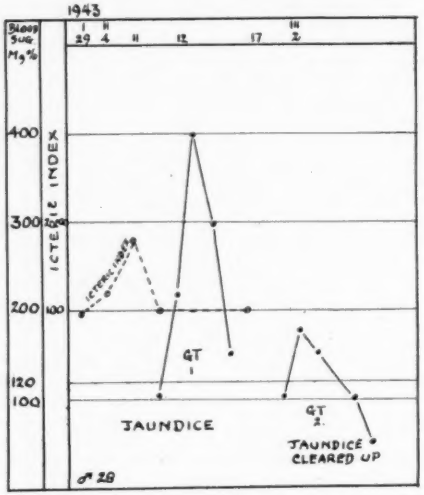


Figure 1 — Case 1

Case Reports

The following cases furnish, I believe, significant data on the problem of the relationship of gall bladder disease and dysfunction of the liver to the production of hyperglycemia and permanent diabetes. In taking the history of any patient, I always inquire whether he or she has ever been jaundiced, ever had attacks of pain in the gall bladder, or has ever been subjected to an operation on the gall bladder. If any such history is present, or if I observe the patient during an episode involving jaundice, cholecystitis or cholecystectomy, I always attempt to obtain detailed information, through repeated observations over a period of long duration, as to the precise effect, temporary or permanent, on the carbohydrate metabolism. The cases here presented exhibit considerable variation in the final effects observed, but they furnish strong evidence that a disturbance of carbohydrate metabolism associated with disease of the liver or gall bladder is always a potential threat that the patient may ultimately become diabetic.

The Effect of Jaundice. Case 1. — Figure 1 shows the results of a glucose tolerance test* performed on a man, aged 28 years, while he was suffering from a severe non-obstructive jaundice. The curve was typical for diabetes; the blood sugar at the end of the third hour was still elevated and the peak reached 400 mg. per cent. At this time the icteric index was 100. A month later, by which time the jaundice had disappeared, the glucose tolerance curve was entirely normal, indicating that the liver storage mechanism was functioning normally.

Case 2. — A readjustment of normal function, however, does not always occur following hepatic jaundice. In one instance, a boy, aged 11 years, became diabetic shortly after the appearance of jaundice. In 1947, when I saw him last, he was aged 34 years, the father of two children and his diabetes was controlled quite satisfactorily by daily dosages of 32 units of protamine zinc insulin.

Case 3. — A man, aged 57 years, had jaundice with fever, and within three months, persistent diabetes appeared.

These last two cases indicate that liver affections can and at times do lend to diabetes, and that patients so affected

*Unless otherwise indicated, all glucose tolerance tests were performed by determination of blood sugar at the time of ingestion of 100 grams of glucose with the patient fasting and at intervals of one-half, one, two, three and four hours afterward.

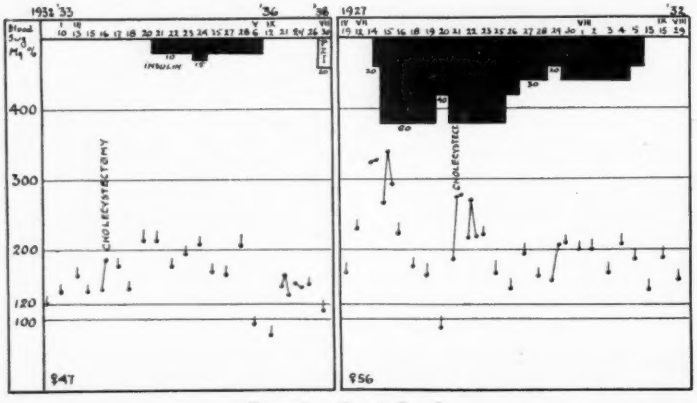


Figure 2 — Case 4, Case 5

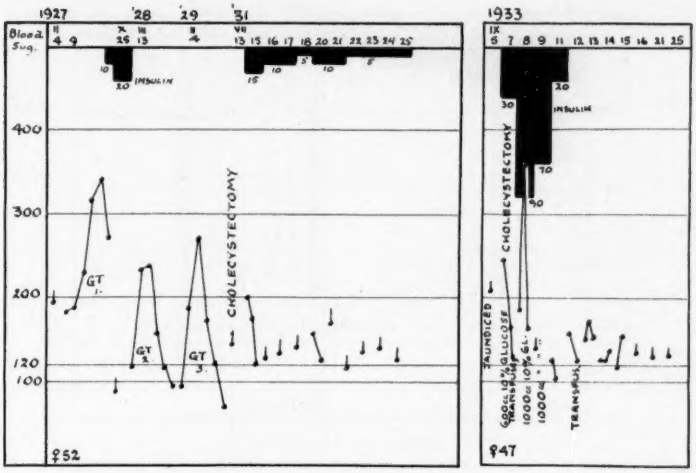


Figure 3 — Case 6, Case 7

should be carefully observed so that any tendency toward diabetes may be discovered as early as possible.

The Effect of Cholecystectomy on the Level of the Blood Sugar. Case 4. — The first chart in Figure 2 is that of a woman, aged 47 years, who exhibited a slight disturbance in carbohydrate metabolism. After cholecystectomy and a small dosage of insulin for fifteen days, normal function was restored and the patient took no insulin for four years. When I saw her in 1938, five years after the operation, she was taking 20 units of protamine zinc insulin for the control of her diabetes. In this instance, apparently the cholecystic disease did upset the carbohydrate metabolism sufficiently that frank diabetes resulted eventually.

Case 5. — The second chart (Fig. 2) shows the clinical course of a woman, aged 56 years, who had a much more serious disturbance of the carbohydrate metabolism just before and after cholecystectomy. Large doses of insulin, up to 60 units, had to be used to achieve reasonable control. After removal of the gall bladder, the blood sugar level became lower, and the insulin requirement was constantly reduced until two weeks after operation when it was discontinued altogether. When the patient was last seen, five years after the operation, the fasting blood sugar was approximately normal, without insulin.

In both of these patients, considerable improvement in carbohydrate metabolism followed cholecystectomy. In the first case, in which the metabolic disturbance seemed relatively mild, frank diabetes resulted five years later; in the second case, in which the upset was apparently more severe, there was almost complete restoration of function after the same length of time.

Case 6. — A woman, aged 52 years, was first seen on February 4, 1927. She had a history of having had typhoid fever and complained of recurrent severe attacks of pain in the epigastrium radiating to the back, and lasting ten to thirty minutes, accompanied by tarry stools. For three years, she had had episodes in which these attacks would recur nearly every day for a week, and then would disappear for a time. When she was first examined, the blood sugar level was 194 mg. per cent four and one-half hours after a meal. She was obese; her weight was 161 pounds and her height 56 inches. The blood pressure was 150 systolic, 90 diastolic. A glucose tolerance test (Fig. 3) showed a definitely diabetic condition.

She was placed on a diet of 100 grams of carbohydrate, 60 grams of protein, 128 grams of fat, with a total of 1800 calories, and was instructed to take 10 units of insulin each morning and 10 units each evening.

When she was examined eight months later, on October 25, 1927, the fasting blood sugar was 88 mg. per cent, and insulin was discontinued. Five months afterward (March 13, 1928), a second glucose tolerance test showed considerable improvement over the first, but still resulted in a prediabetic type of curve. Nearly a year later (February 4, 1929), a third glucose tolerance test gave practically the same results. She was continued on dietary treatment, without insulin. On July 13, 1931, a cholecystectomy was performed, after which she received a small amount of insulin. The diabetic condition was controlled on 5 units daily.

The improvement in the diabetic state after cholecystectomy in this case was, I feel, no greater than might have been expected in any other diabetic receiving the same therapy.

Case 7. — A woman, aged 47 years (Fig. 3), was jaundiced and was subjected to cholecystectomy two days after her admission to the hospital. During the postoperative period, it was necessary to administer a considerable quantity of glucose intravenously, with large doses of insulin. After five days, however, all insulin was discontinued and the blood sugar level returned to normal.

This was an acute condition; the patient had cholelithiasis with jaundice which responded promptly after operation and cleared up completely. Unfortunately, there were no additional examinations extending over a period of years so the final outcome is unknown, even though the response at the time of operation indicated a favorable prognosis.

Case 8. — A woman, aged 52 years (Fig. 4), gave a history of having had diabetes for five years when she was admitted to the hospital in February, 1932. Twenty-three years earlier, she had undergone an operation for drainage of the gall bladder and removal of gall stones. During the past seven years, she had had recurrent attacks of typical gall stone colic; in one of these attacks, jaundice had developed. In February, 1931, she had a very serious attack, was severely jaundiced, and suffered from chills and fever (102° F.). Although she was hospitalized, no operation was performed at that time. After she returned home, she had several more attacks and lost considerable weight. During this period, immediately preceding her admission to our hospital, the 25 units of insulin that she had been taking for control of her diabetic condition was discontinued, although her diet was regulated strictly during that time.

When I first examined her, the fasting blood sugar was 243 mg. per cent and she exhibited a heavy glycosuria. Insulin was administered in doses of 30 and 35 units a day, and a cholecystectomy was performed two days later. After the operation, the insulin requirement decreased; three months later she was taking only 10 units a day and the blood sugar was normal.

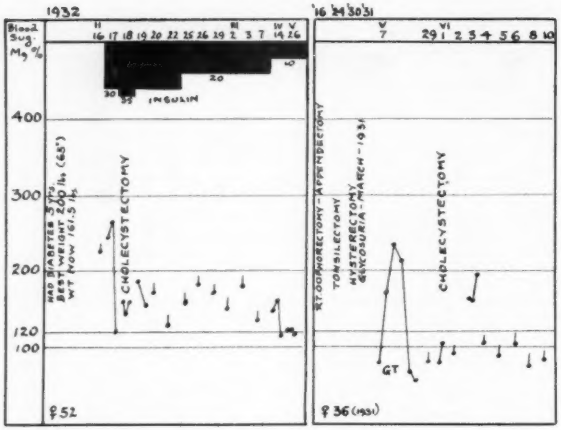


Figure 4 — Case 8, Case 9.

This case shows that removal of an infected gall bladder, even when the disease has been of long duration, may bring about a marked improvement in the diabetic condition.

Case 9. — A woman, who was aged 31 years in 1931 (Fig. 4), had begun to have pain in the right upper quadrant in November, 1930. The pain was dull with occasional exacerbations of sharp, severe pain. There was no jaundice, but for two months she had been vomiting bile about every two weeks. Glycosuria had been present since March, 1931.

Two months later, a glucose tolerance test on admission showed a prediabetic curve, but until cholecystectomy was performed three weeks later, the fasting blood sugar was normal. After operation, there was a temporary rise in the blood sugar, but this receded promptly without insulin and stayed normal thereafter.

This case raises the question as to whether a delay in the performance of cholecystectomy might have resulted in the development of a frank diabetes. Since the glucose tolerance curve showed some abnormality at the beginning, it is quite possible that in time this would have happened. However, since the condition was of short duration and mild, the patient had only a slight temporary derangement of the carbohydrate metabolism.

Case 10. — Diabetes had been discovered in a woman, aged 47 years (Fig. 5), eight months before admission, at which time her blood sugar had been 280 mg. per cent. She had received no insulin. My examination showed hyperglycemia, with blood sugar levels before meals of 214, 194 and 167 mg. per cent and also heavy glycosuria. The diabetic condition was brought under control with insulin, which was discontinued after an operation for dilatation and curettage was performed a week later. Subsequent determinations of the blood sugar showed normal values. Two months later, cholecystectomy and hysterectomy were performed. During the postoperative period, the patient received insulin, but it was discontinued again after four days. During the next three years, the blood sugar level was approximately normal, until 1937, when there was a definite increase. The patient has not been observed since.

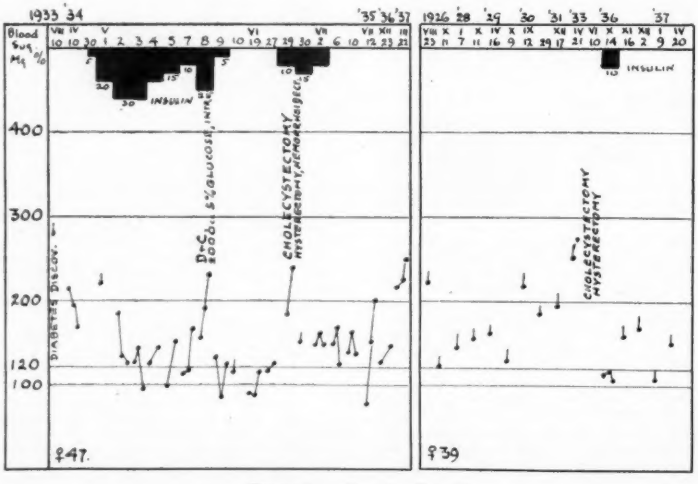


Figure 5 — Case 10, Case 11.

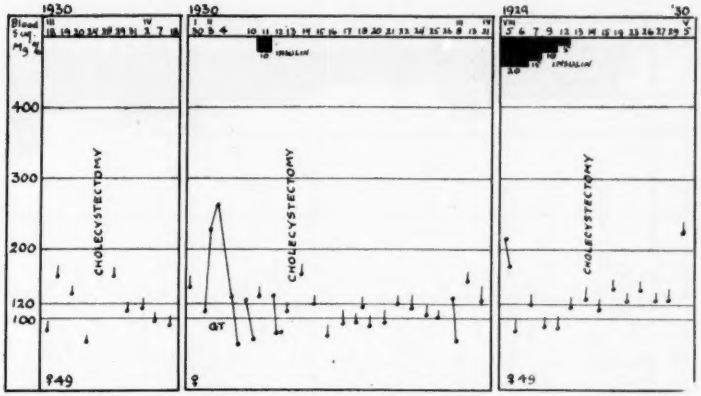


Figure 6 — Case 12, Case 13, Case 14.

Here a relatively mild upset of the carbohydrate metabolism before and following cholecystectomy resulted in a mild derangement of function which persisted after the operation to become a frank diabetic state three years later.

Case 11. — A woman, aged 39 years (Fig. 5), had a mild diabetes in 1926. She did not take insulin, although there was considerable fluctuation of the fasting blood sugar level. In 1933, seven years later, cholecystectomy and hysterectomy were performed. The patient received 10 units of insulin for one day and the carbohydrate metabolism remained much the same as before the operation; certainly it was not aggravated by the episode of gall bladder disease. On the other hand, the mild derangement of carbohydrate metabolism was not remarkably improved after cholecystectomy. In this instance, it would appear that the disease in the gall bladder was not a factor in the development of hyperglycemia.

Case 12. — A woman, aged 49 years (Fig. 6), had a history of severe attacks of pain in the gall bladder region about a year before this record began. Seven months earlier, she had had a severe attack lasting three or four days, with chills and temperature elevated to 104° F. Operation had been performed two and one-half months before, when pus and stones had been found in the gall bladder. The patient went into shock during the operation, so the gall bladder was not removed, but merely drained. Since then she had had attacks of dull pain in the middle epigastrium, radiating to the back. Vomiting usually relieved these attacks. The

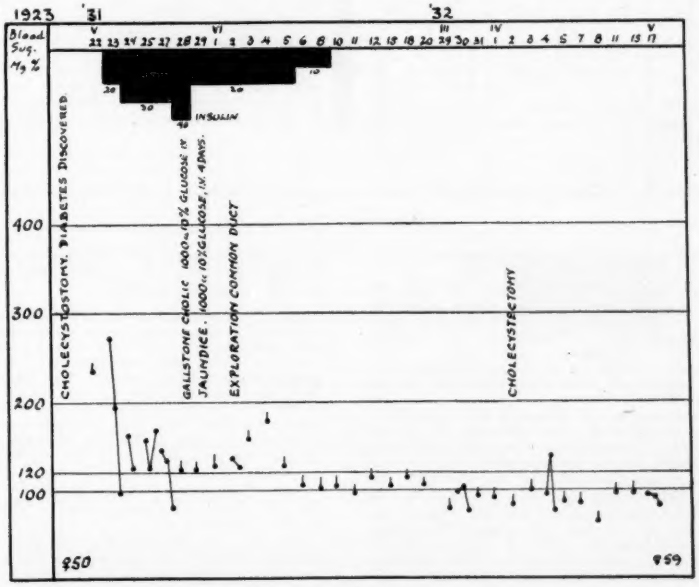


Figure 7 — Case 15.

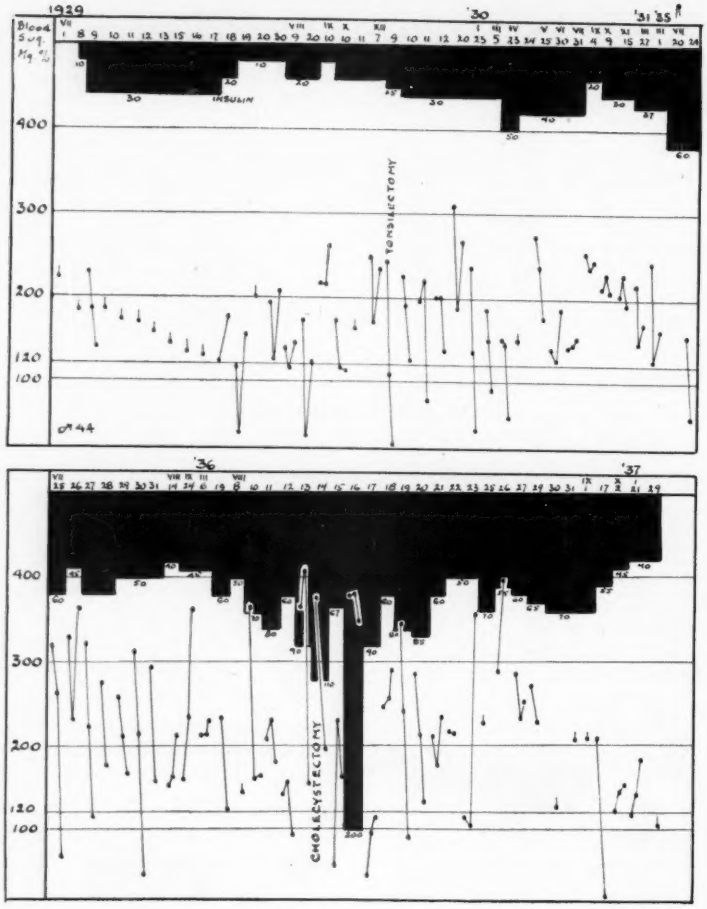


Figure 8 — Case 16.

pain appeared every other day and continued three to four hours, and had no relation to meals.

When the patient was first seen on March 18, 1930, the first blood sugar was normal; then there was a slight elevation on several occasions, but after cholecystectomy, with one exception, blood sugar determinations were normal throughout her stay in the hospital.

In this case, a severe infection of the gall bladder, with stones, failed to produce any permanent disturbance of carbohydrate metabolism.

Case 13. — Detailed notes are missing in this case, but it is very similar to the preceding one. Although the glucose tolerance curve was abnormal before operation, there was no marked abnormality during the postoperative period and blood sugar levels remained normal after the operation.

Case 14. — An obese woman, aged 49 years, complained of pain in the back and stated that she had had diabetes for some time which had been treated with insulin. The dosage was gradually reduced from 20 to 5 units daily during the seven days that she was under observation before operation and then was discontinued entirely. The blood sugar levels remained normal for nine months after cholecystectomy, but then showed some increase.

This patient was a mild diabetic whose carbohydrate metabolism improved following cholecystectomy but eventually reverted to a diabetic status.

Case 15. — Figure 7 shows data on a woman who, in 1923, at age 50, had undergone a cholecystectomy which had been performed elsewhere. At that time a diagnosis of diabetes was also made. Her treatment had consisted only of a restricted diet. When she was first examined, on May 22, 1931, the blood sugar was 242 mg. per cent, so the next day insulin was administered and continued for two weeks, during which time she was having gallstone colics and became jaundiced. On June 2, 1931, an exploratory operation on the common duct was done. After the eighth postoperative day, all insulin was discontinued and the blood sugars remained normal. When she returned a year later for a cholecystectomy, the level of the blood sugar was still normal and remained so after the operation.

Case 16. — A man, aged 44 years (Fig. 8), had glycosuria, discovered in 1929. He had been treated by a restricted diet for several months, and had lost 27 pounds. On admission, the fasting blood sugar was 222 mg. per cent four hours after a meal and there was no glycosuria. Treatment with insulin

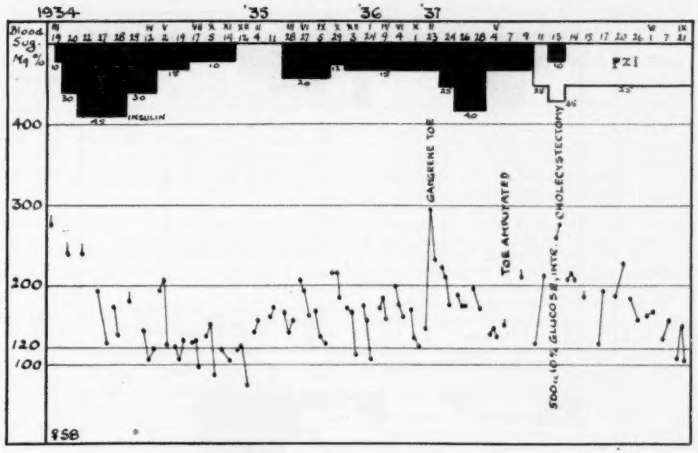


Figure 9 — Case 17.

was instituted but there was much fluctuation of the blood sugar, despite increased dosage up to 90 units a day.

Seven years later (August 14, 1936), a cholecystectomy was performed. After this, there was improvement in the diabetic condition, although the level of the blood sugar still fluctuated considerably for four months. Then satisfactory stabilization was achieved with an insulin dosage of 40 units daily.

This is an instance in which a patient with severe diabetes exhibited definite improvement after cholecystectomy.

Case 17. — A woman, aged 58 years, had diabetes which had developed recently and was brought under control readily with diet and insulin. Within a few months, insulin was discontinued for a time but later had to be resumed. Three years later, gangrene of a toe developed and required amputation. A short time afterward, a cholecystectomy was performed. Following this, the level of the blood sugar was stabilized on a steady dosage of 25 units of protamine zinc insulin (Fig. 9). Unfortunately, my observations extended only a few months after operation, so the final outcome in this case is not known.

Case 18. — Diabetes had been discovered in a single woman, aged 57 years, four weeks prior to this record (Fig. 10). Her father had died of diabetes. At the outset, in 1928, the fasting blood sugar was 134 mg. per cent and there was but a faint trace of sugar in the urine. Administration of insulin for four days brought the blood sugar to normal, and the drug was then discontinued. The level of the blood sugar was normal at subsequent examinations for a year and a half. Then iritis developed, in 1930, and insulin had to be resumed in increasing dosage, up to 50 units a day. The patient was in the hospital and her temperature was elevated. Cholecystectomy was performed for stones which had been revealed roentgenographically. After the operation there was much fluctuation in the level of the blood sugar, even when 60 units of protamine zinc insulin were given and with regular insulin added.

This status continued for ten years, when thrombophlebitis of the left leg appeared and the insulin dosage had to be steadily increased. She had fever during this time and died on March 18, 1940. Necropsy revealed a primary carcinoma of the liver.

In this case there was but little, if any, improvement following cholecystectomy, obviously because of derangement of liver function owing to carcinomatosis. At the beginning, this patient's diabetes was extremely mild, and remained so for two years, when the gall bladder disease aggravated the diabetic condition definitely and severely.

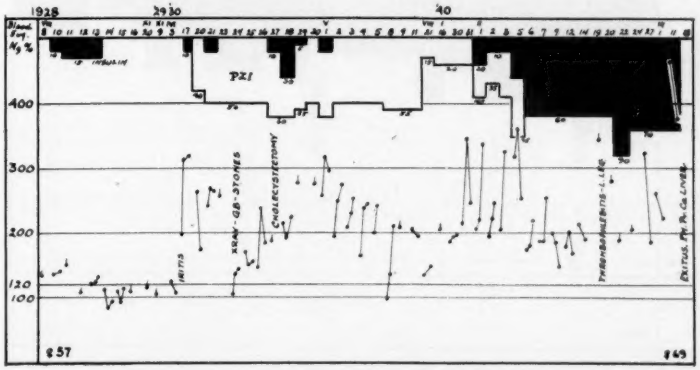


Figure 10 — Case 18.

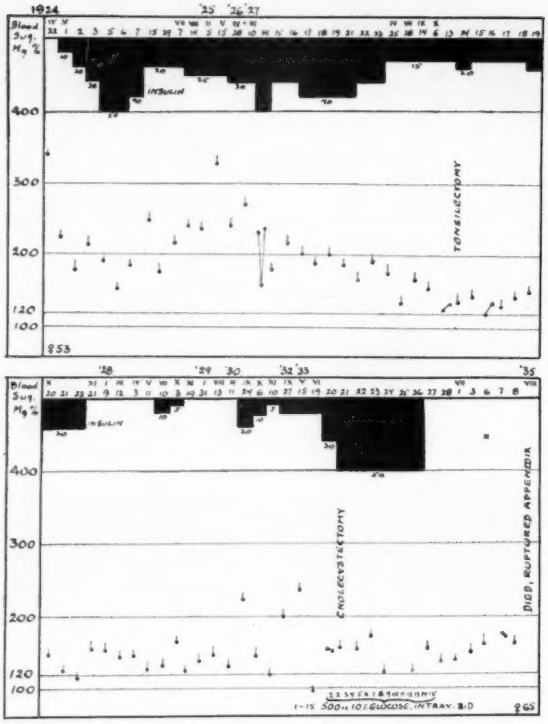


Figure 11 — Case 19.

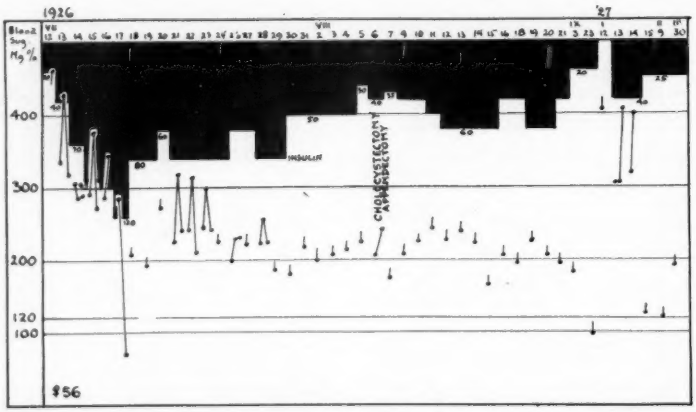


Figure 12 — Case 20.

Case 19. — A woman, aged 53 years, had had symptoms of diabetes for three or four months prior to this record (Fig. 11), and had lost considerable weight. On admission, the level of the blood sugar was 340 mg. per cent and the sugar in the urine was 4 per cent. Even with insulin treatment, there was considerable fluctuation of the blood sugar, as she did not adhere to the diet prescribed during this time. Three years later, after a tonsillectomy, the blood sugar became stabilized and it was even possible to discontinue the insulin at intervals. In 1933, nine years later, a cholecystectomy was performed, after which all insulin was discontinued, with a fairly good control of the diabetic condition until two years later, when she died of a ruptured appendix.

Here cholecystitis developed in a patient with diabetes of long duration and apparently did not aggravate the diabetic condition; as would be expected under these circumstances, there was no appreciable change in the diabetic state after cholecystectomy.

Case 20. — A single woman, aged 56 years, whose past history was entirely negative, was first seen on July 12, 1926 (Fig. 12) with the complaint that for fifteen months she had had recurrent pain in the right side of the abdomen, accompanied by vomiting. There was tenderness over the gall bladder region, but the pain was not excessively severe. She had lost 30 pounds during this period. Each attack lasted about three days and soreness over the abdomen persisted afterward. Her appetite was impaired and for about three months she had been on a restricted diet because of heavy glycosuria which had been discovered about a year after the first attack of abdominal pain. Although the urine had been free of sugar during the first year of her illness, she had noted excessive thirst throughout the preceding winter.

Her height was 65 inches and her weight at the time of examination was 110 pounds. Her blood sugar was 460 mg. per cent. Large doses of insulin were administered, but the level of the blood sugar was not satisfactorily controlled. On August 6, about three weeks after admission, cholecystectomy and appendectomy were performed. After this, there was a general drop in the level of the fasting blood sugar and it was possible to diminish the insulin dosage somewhat. When the sugar in the blood reached a level below 100 mg. per cent, the insulin was discontinued temporarily to see what could be accomplished by diet alone, but a recheck two months later revealed that the blood sugar had climbed to more than 400 mg. per cent, and insulin had to be resumed. This time, however, it was given in a smaller total dosage than before the operation. Hence it is justifiable to state that the removal of the gall bladder improved the diabetic condition to some extent, as judged by the insulin requirement.

Case 21. — A single woman, aged 55 years, had experienced the menopause twenty years earlier. Her maternal grandmother had died of diabetes. Her clinical history included the infections of childhood, typhoid fever at age 18, rheumatism and influenza. She had been jaundiced a year before admission.

She was first seen on December 16, 1925 (Fig. 13), when she said that diabetes had been discovered in August, 1924. At that time she had had the classical symptoms and a blood sugar of 340 mg. per cent. Her physician had given her insulin for ten days. The jaundice had developed shortly afterward and had cleared up in six weeks. On December 6, 1924, jaundice had reappeared; at that time she was hospitalized and received insulin for a week, but was discharged on dietary treatment alone. Her weight had been 175 pounds in August, 1924; when I examined her on December 16, 1925, she weighed 107 pounds and her height was 63 inches. Just before she consulted me, she had been taking 10 units of insulin daily and was having reactions every day but had been sugar-free for two months.

Because of the reactions and also because the blood sugar level was normal, I discontinued the administration of insulin on January 1, 1926, while she was still in the hospital under observation. As the record shows, the blood sugar level remained normal throughout the day. However, when a glucose tolerance test was performed on January 18, 1926, this was definitely of the diabetic type. She continued treatment on diet alone, but when she was re-examined on March 25, the blood sugar was elevated to 250 mg. per cent. Since she was then in the hospital for a cholecystectomy, I began the administration of 20 units of insulin, which was later increased. The blood sugar promptly returned to normal on 35 to 40 units of insulin daily. Cholecystectomy was performed on March 29, 1926, and after this, glucose solution, 10 per cent, was given in amounts of 250 cubic centimeters twice a day for a week, and there was no elevation of the blood sugar level during that time. She was discharged from the hospital on April 19, again on diet alone, without insulin. During the next three years, there were occasional elevations of the blood sugar; insulin was used on two occasions, in August, 1926, for three months, and in June, 1927, just one injection was given. At the end of 1928 and in 1929 the patient was continuing on dietary treatment, the blood sugar was normal and she was feeling well.

The diabetic condition in this instance was unstable before operation. Afterward, there remained some instability, but the condition was satisfactorily controlled on diet alone and for a year the blood sugar remained normal. Apparently the diabetic status, following the operation, was improved somewhat although the change was not spectacular. It is perhaps worthwhile to point out that during the week after operation, the blood sugar was normal throughout the day.

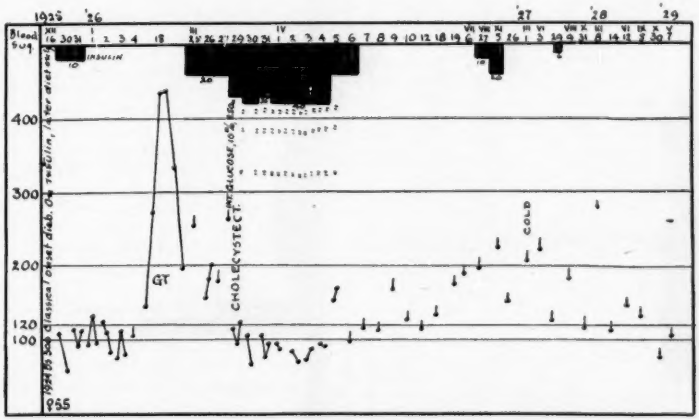
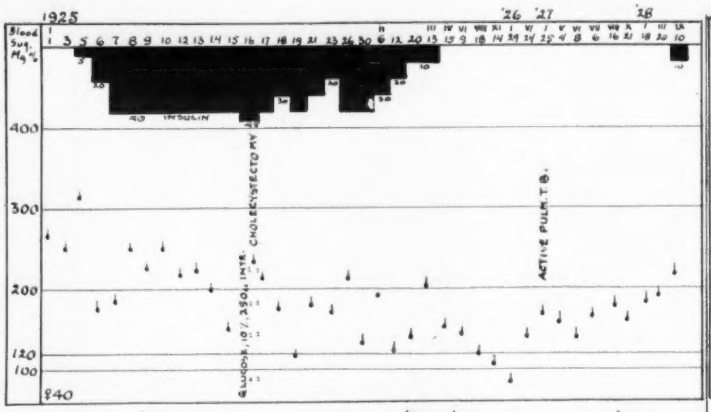


Figure 13 — Case 21.



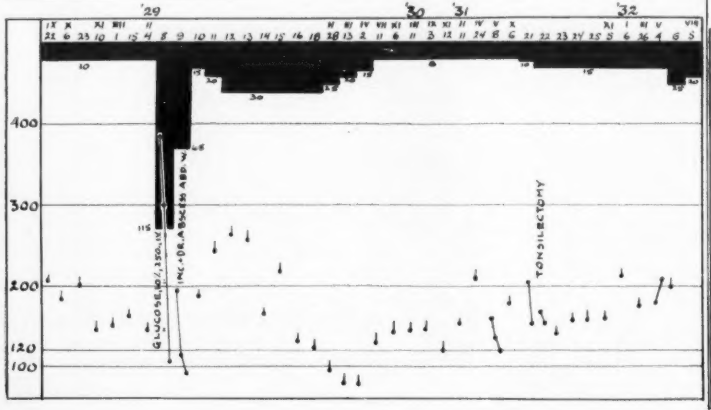
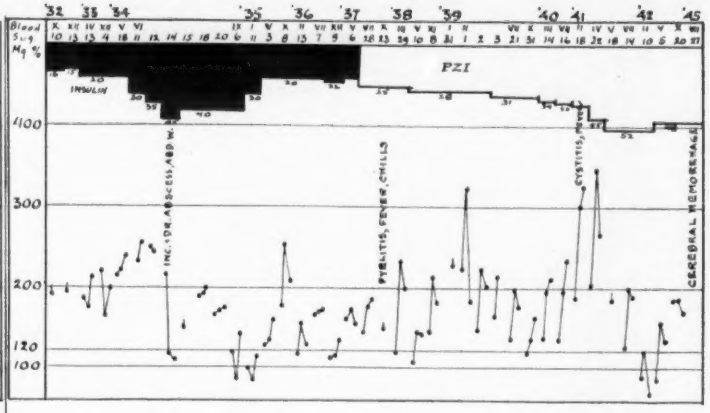


Figure 14a — Case 22.



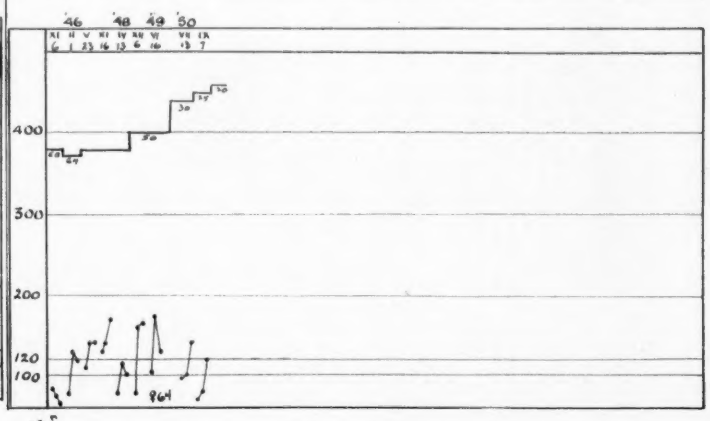


Figure 14b — Case 22.

Case 22. — A woman, aged 40, was first seen in 1925 (Fig. 14) with a history of recurrent gall-stone colic for eighteen years and had typical symptoms of diabetes. Glycosuria had been discovered eight years previously and after that, she had been on a restricted diet. At the time of admission, she was intensely jaundiced. The fasting blood sugar at that time was 266 mg. per cent. Insulin was administered, and after eleven days, the fasting blood sugar was nearly normal, and cholecystectomy was performed. After the operation, the diabetic condition improved and in March, 1925, the insulin was discontinued and the blood sugar remained at a satisfactory level until 1927, when pulmonary tuberculosis developed. It is now twenty-four years since the gall bladder was removed, the patient is aged 64 and fairly active.

In this case the diabetic condition certainly did improve after cholecystectomy. Nevertheless, it is interesting to note that although this patient was extremely conscientious in regulating her diet, still, with advancing age, from 1935 on, her insulin requirement increased.

COMMENT

These twenty-two cases illustrate the variations of hyperglycemia in jaundice and gall bladder disease, and in most of them, prolonged observations revealed the final outcome.

Generally speaking, it is plain that the disturbance of carbohydrate metabolism during jaundice or during an acute cholecystitis is not just a coincidence which "belongs" to these affections as the result of an imbalance in the liver storage mechanism. It is more than that. Whether the toxemia alone causes the hyperglycemia, through whatever mechanism this occurs, i. e., by derangement of the mechanism of storage of glycogen in the liver or the blocking of the action of insulin (endogenous or exogenous), it appears that in the majority of cases this prolonged hyperglycemia has a deleterious effect on the islands of Langerhans, since permanent diabetes does result usually if the observations are extended over a long enough period. In experimental work on animals, Dohan and Lukens and others have shown that a prolonged hyperglycemia, if unchecked, produces anatomic changes in the islands of Langerhans, such as are seen in diabetes. It is likely that the same mechanism may be operative in producing eventually the large group of permanent diabetics in patients with a history of disease of the gall bladder, even in those who have been subjected to cholecystectomy. It is hard to conceive that the hyperglycemia in these cases is merely accidental, and due entirely to the disturbance in the liver storage mechanism. Those who advocate administration of high-carbohydrate diet during the period of the disturbance in carbohydrate metabolism, without insulin, do observe, it is true, a clearing of the condition at times after the operation. But what is the final outcome in these patients? This is the point which I have tried to emphasize in presenting these prolonged observations, since the final outcome often is quite different from that observed immediately after the cholecystectomy. As these records show, the picture is not an encouraging one. I think it behooves us to respect hyperglycemia, no matter what its cause, and to try to counteract it by means at our disposal rather than to trust to luck, hoping that all will be well. Such patients need to be followed carefully for years after a cholecystectomy to make sure that all *is* well.

Incidence of Gall Bladder Disease in Diabetics. As has already been noted in the discussion of the literature, the association of cholecystitis and diabetes has been a subject of comment and study for the past fifty years, and various observers have reported a relatively high incidence of cholecystic disease among diabetic patients, as compared to the general population. Joslin (33) and Wilder (34) reported an incidence of 5.4 per cent of gall stones among their diabetic patients; Joslin's series numbered 5,400 and Wilder's, 2,584.

In the records of 6,000 diabetic patients that I have observed personally, the incidence of gall bladder disease is somewhat higher than that reported by Joslin and Wilder, although the number with cholelithiasis, as judged by the history of the typical colic or cholecystectomy, is approximately the same, that is, 5.08 per cent. In my series there were in addition 104 patients with a history of jaundice. When these are added to the 305 patients who had gall bladder attacks or cholecystectomy or both, the total number of patients with infection of the gall bladder is 409, or 6.81 per cent of the total series of 6,000 patients. More detailed information regarding these patients is shown in Table 2. It is interesting to note that the incidence according to sex is approximately four to one for females and males. This preponderance in females is not surprising in view of the fact that also among nondiabetics, gall bladder disease is much more common in women than in men.

TABLE II

OBSERVATIONS ON GALL BLADDER INFECTION IN 6,000 CASES OF DIABETES (JOHN)

Decade	*Sex*	*Jaundice*	*Gall Bladder Attacks*	*Gall Bladder Operations*	*Total*
I	M	7			
	F	7			14
II	M	3			
	M*	1			
	F	6	1	2	13
III	M	5			
	M*	1			
	F	11	9	4	30
IV	M	6	6	3	
	M*		1		
	F	5	20	18	
	F*		7	6	72
V	M	2	7	4	
	M*	1	1		
	F	13	43	24	
	F*	1	10	5	111
VI	M	4	15	6	
	F	17	45	25	
	F*		5	2	119
VII	M	6	5	1	
	F	3	17	7	
	F*		4		43
VIII	M	2			
	F	3	1	1	7
Total	M	38	35	14	87
	F	66	162	94	322
	Both	104 (1.73%)	197 (3.28%)	108 (1.8%)	409 (6.81%)

*Diabetes and Hyperthyroidism

SUMMARY

Since the proper understanding of the relationship between gall bladder infections and diabetes is an important one from the standpoint of the management of such patients, this presentation is offered with the hope of throwing added light on the subject. Detailed observations on twenty-two patients, most of them over a prolonged period of years, have been furnished to show that there is considerable variation in the effects of cholecystic disease on carbohydrate metabolism in different individuals. However, it seems obvious that any disturbance or impairment of liver function as indicated by decreased glucose tolerance represents a definite threat that ultimately the patient may become diabetic. Removal of an infected gall bladder often improves the carbohydrate metabolism in such cases, but it does not always insure that this improvement will be permanent.

A brief resume of the literature on the relationship of cholecystitis and diabetes, including clinical observations, experimental studies and various interpretations of these, has been presented as background and comparison for my own observations and opinion.

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THE PROGNOSTIC SIGNIFICANCE OF NOCTURNAL GASTRIC SECRETION IN ULCER PATIENTS

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INTRODUCTION

THE PURPOSE of this paper was to determine if any prognostic significance could be attached to the volume and acidity of nocturnal gastric secretion in patients with duodenal ulcer. Work by other investigators has shown that the volume and acidity of nocturnal gastric secretion is generally higher in patients with active duodenal ulcer than in normal controls. Winkelstein (10) performed continuous gastric aspirations during the night on a series of 169 cases in which he showed there was a definite increase in the volume and acidity in active duodenal and gastric ulcer patients compared with normal subjects. Similar results have been obtained by Palmer et al. (1, 3, 4, 5, 6), Dragstedt and coworkers (1, 2, 8), and Val Dez (9).

However, in studies not entirely comparable (sub-

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jects were ambulatory ulcer patients with mild symptoms), Sandweiss and his group (7) found that the average volume and acidity of nocturnal gastric secretion was approximately the same in ulcer patients as in normal controls. Therefore, it also became of interest in this study to compare the night secretion in ulcer and normal patients, and to relate the volume and acidity of the secretion to the patients' symptoms.

MATERIALS AND METHODS

This study consists of an analysis of hourly nocturnal gastric secretion in 13 duodenal ulcer patients (20 studies) and 9 non-ulcer patients (9 studies). In addition, continuous 12-hour aspirations were done in 15 duodenal ulcer patients (31 studies) and 6 non-ulcer patients (6 studies), making a total of 28 ulcer patients with 51 aspirations, and 15 non-ulcer patients with 15 aspirations. All of the patients were males, ages ranging from 20 to 55 years. All studies were initiated within 5 days after admission, before there had been any definite clinical improvement.

All of the ulcer patients had clinical symptoms severe enough to cause them to seek hospitalization, and all had definite roentgenologic evidence of duodenal ulcer. Included in the group were both chronic cases with reactivation of symptoms and cases never previously diagnosed.

The non-ulcer patients were all on the gastrointestinal service, having been admitted for a variety of functional complaints. Roentgenologic studies of each of these patients were normal. Three of these patients had symptoms compatible with duodenal ulcer; another had a history of a previously perforated duodenal ulcer. The remainder of the cases were diagnosed as having functional gastro-intestinal disturbances.

The method consisted of passing a Levine tube at 8 p. m., and all gastric contents which were obtained at this time were discarded. The tube was then connected to a continuous suction apparatus, and collecting bottles were replaced every hour until 8 a. m. In those cases where continuous 12-hour aspirations were done, the entire specimen was collected in one bottle.

No patient was allowed anything by mouth after 5:30 p. m., nor were any sedatives or narcotics administered during the period of aspiration. On the day of the procedure, the patients were fed the diet prescribed for them by their ward physician, no effort being made to serve a controlled diet.

In any instance where excessive bile was obtained, the specimen was discarded.

Titration was done according to accepted procedures, using 1/10 N NaOH, with Toepfer's reagent as the indicator.

RESULTS

The total 12-hour volume of gastric secretion obtained by continuous suction is shown in Figure 1. It is apparent that the ulcer patients showed definitely greater volumes. In 51 aspirations in the 28 ulcer patients, the volumes were over 600 cubic centimeters in 45 aspirations (23 patients). In the 15 aspirations in the 15 controls, only 5 were above 600 cubic centimeters. Of the 5 controls with a night volume over 600 cubic centimeters, two gave histories typical of duodenal ulcer, but roentgenologic studies were negative. One had a history of perforated ulcer but negative x-rays at the time of this study, and one gave an unconfirmed story of ulcer found by x-ray five years before coming to this hospital. Of the 5 ulcer patients with volumes below 600 cubic centimeters, three in other determinations showed volumes over 600 cubic centimeters.

The total free hydrochloric acid, expressed in milligrams, is shown in Figure 2. In the duodenal ulcer

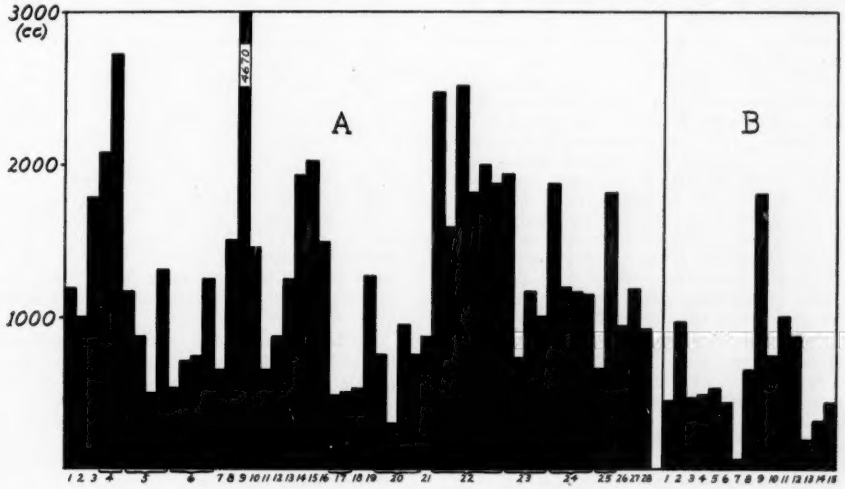

Fig. 1. Total volume gastric secretion during night
A = ulcer patients, B = controls

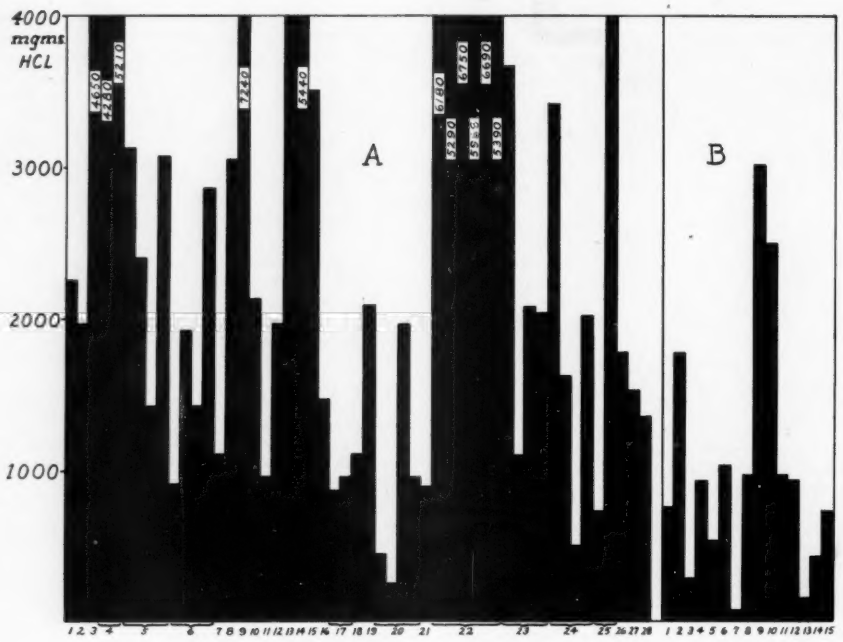

Fig. 2. Total mgms. HCL secreted during night
A = ulcer patients, B = controls

group, 41 aspirations (21 patients) contained more than 1,000 milligrams, and in only four aspirations (3 patients) was there less than 700 milligrams. In the control group, none except the five patients previously cited secreted more than 1,000 milligrams of hydrochloric acid, and only an additional three secreted over 700 milligrams.

In 20 consecutive studies in 13 ulcer patients and eight consecutive controls, the geometric mean of the milligrams of hydrochloric acid in the specimens collected in hourly periods was computed. The results are tabulated in Figure 3. The level of secretion was significantly higher throughout the night in the ulcer cases. The high values in both groups obtained at 9 p. m. are attributed to the evening meal and the stimulus of the tube itself. A terminal rise occurred after the patients awoke in the morning, and it might be noted that trays were being served to fellow patients at that time. A significant rise occurred only in the ulcer cases at 5 a. m.; whereas, there was no significant change in the control group.

An arbitrary level of acidity had to be selected in order to determine whether the night secretion of ulcer patients could be used to prognosticate the response to medical therapy.

Kirsner, et al. (4), in their report of five cases with intractable ulcer and intractable hyperacidity, obtained values for night aspirations ranging from 3,000 to 6,000 milligrams of hydrochloric acid. Accordingly, 3,000 milligrams of hydrochloric acid were selected as a baseline for predicting the possible intractability of the ulcer and subsequent surgical intervention.

Of 12 of our ulcer patients (19 titrations) whose night secretions were 3,000 milligrams or more, only four required surgery. Of these four, one required surgery because of partial pyloric obstruction and one because of recurrent hemorrhage. The remaining two required surgery because of intractable pain. One of these failed to respond to strict hospital medical ulcer management, and the other could be controlled while in the hospital but had recurrence of severe pain on each occasion when he returned to work. Both these latter patients had very high values ranging from 4,650 to 6,750 milligrams of hydrochloric acid (Cases 3 and 22 in Figure 2). The eight remaining patients in this group responded promptly and adequately to medical management. It is to be noted that, in this latter group where more than one aspiration was done, the majority of determinations fell below 2,000 milligrams of hydrochloric acid.

Although this series is small, it would seem that, on the basis of one determination showing hyperacidity (3,000 milligrams or more), it is impossible to predict the response to medical management or the need for surgical intervention. However, where there is persistent, marked hyperacidity, as determined by multiple aspirations, failure of medical management would seem likely.

Three patients in our series who did not show extreme hyperacidity also required surgery, two for re-

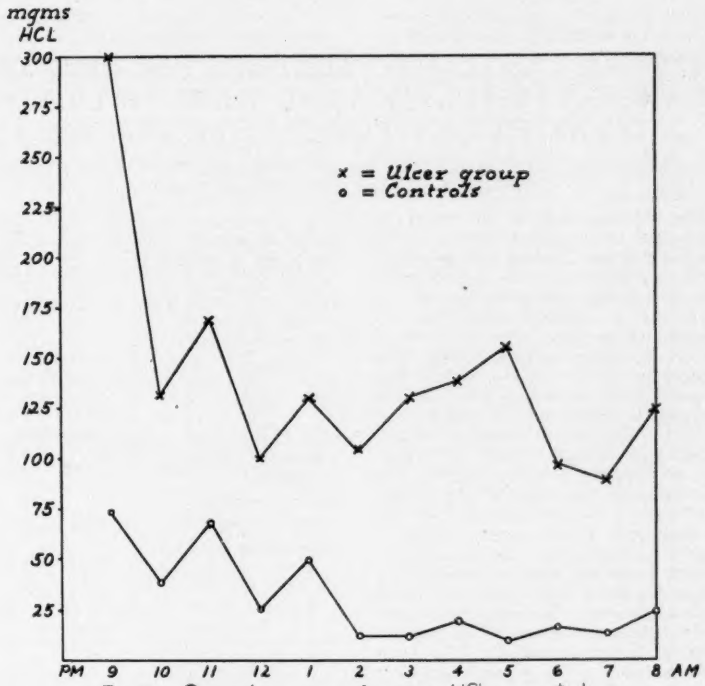

Fig. 3. Geometric mean of mgms. HCL secreted hourly in 13 ulcer patients (20 studies) and 9 non-ulcer patients (9 studies).

current hemorrhage and one for marked gastric retention. Obviously, not all complications of duodenal ulcer are associated with excessive hyperacidity.

As shown above (Figure 2), the acidity of the night secretion in the ulcer patients was considerably greater than in the control group. In the well-controlled study by Sandweiss et al. (7), there was no significant difference in the night secretion between ulcer patients and controls, but admittedly, in their study, the ulcer patients were all ambulatory and had minimal symptoms. It would therefore seem justifiable to conclude from this study that the severity of symptoms parallels the degree of acidity in the night secretion, again confirming the interrelationship of acidity and ulcer.

SUMMARY

1. Total night gastric secretion was studied in 28 patients with duodenal ulcer and 15 controls; hourly studies were done in 13 patients with duodenal ulcer and nine controls.

2. The volume and acidity were significantly higher in the ulcer cases throughout the night. The majority of ulcer patients secreted more than 600 cubic centimeters of gastric fluid containing more than 1,000 milligrams of hydrochloric acid; whereas, most of the controls secreted less than 600 cubic centimeters of fluid and less than 1,000 milligrams of hydrochloric acid.

3. A direct relationship apparently exists between the severity of symptoms and the degree of nocturnal acidity.

4. In cases where multiple nocturnal aspirations reveal persistent extreme hyperacidity (above 3,000 milligrams of hydrochloric acid), medical management may be expected to fail. Such hyperacidity may afford an additional prognostic guide in the management of patients with duodenal ulcer.

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A STUDY OF LABORATORY METHODS FOR DIAGNOSING ENDAMOEBA HISTOLYTICA AND THEIR APPLICATION TO 5,048 PERSONS FROM THE CHICAGO AREA

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THE PAPERS and discussion of the panel on amebiasis presented at the annual meeting of the American Society of Tropical Medicine in 1949 pointed out even more clearly than heretofore the difficulties and disagreements existing among recognized experts on the subject of amebiasis. To quote Dr. Sodeman, a member of the panel, " . . . . it would appear that no one is willing to agree on the same test, how it should be run or what it means. The physician is forced to go to the bedside with a definite report based on variable standards on which none . . . seem to agree." (1) Dr. Bargen, speaking recently before the Illinois State Medical Society in Chicago, stated: ". . . . the evidence indicates that this disease has been somewhat neglected in the United States." (2) In view of the discrepancies cited, and the undoubted importance of this protean disease, it seemed advisable to present together in one paper the results of extensive experience with Endamoeba histolytica in Cook County, Illinois with patients of varied backgrounds, including a careful analysis of the studies undertaken by the authors during that period to determine the efficacy of laboratory methods. The latter deserve particular attention as all persons engaged in diagnostic parasitology will agree and as has so frequently been mentioned, the reliability of techniques employed for diagnosis largely determines the percentage of positive findings. An attempt was also made to review microscopic elements found in fecal specimens in amebiasis as compared to both shigellosis and salmonellosis.

In the first series of experiments a study was made of methods used for the detection of Endamoeba histolytica in stools. It is presented first as an aid to evaluation of all following studies. The investigation consisted of the study of one stool specimen each, collected from 617 patients with chronic diarrhea. The specimens were examined by saline and D'Antoni's (3, 4) iodine smears, Quentzel's stain (5), cultivation in two tubes of Dobell and Laidlow's medium (6), two permanent hematoxylin smears stained with a modified Ratcliffe and Parkins (7, 8, 9) procedure and the zinc sulfate flotation of Faust (10). Table 1 shows the probability of success or failure of the methods employed and evaluates combinations of the techniques. The results correspond closely to the findings of Faust (11) in demonstrating the superiority of the zinc flotation and the hematoxylin stain. The great value of hematoxylin stains was established also by other observers. Weinrich (12), e. g., had found in a survey of 1,060 college freshmen that 34.5 per

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TABLE 1.

COMPARISON OF METHODS USED FOR THE DETECTION OF E. HISTOLYTICA IN FIRST STOOL SPECIMENS FROM 617 PATIENTS WITH CHRONIC DIARRHEA

1. Using Methods Alone:

Method of examination	*No. positive*	*Probability of (+) finding*	*No. of failures*	*Probability of failure*
Saline and iodine smears	42	.41	61	.59
Quentzel stain	44	.43	59	.57
Culture (Dobell-Laidlow)	68	.66	43	.44
Hematoxylin stained slides	91	.88	12	.12
Zn flotation	96	.93	7	.07

2. Evaluation of combinations of methods:

Combination of methods and result	*# positive*	*% positive*
Only culture positive, hematoxylin slides and flotation negative	1	.9
Only slides positive, culture and flotation negative	6	5.8
Only flotation positive, culture and slides negative	11	10.7
Hematoxylin slides and flotation positive	102	99
Total	103	16.7

TABLE 2.

COMPARISON OF METHODS USED FOR THE EXAMINATION OF PROCTOSCOPIC SPECIMENS FROM 428 PATIENTS WITH CHRONIC DIARRHEA

Method of examination	*# positive*	*Probability of (+) finding*	*This method alone effective; others failed*	
			#	%
Saline and iodine smear	21	.28	0	0
Culture (Balamuth)	53	.70	0	0
Hematoxylin stained slides	69	.91	15	19.7
Zn flotation	61	.81	7	9.2
Total positive	76 = 17.7%			

cent of the amebic infestations detected by the use of such slides were missed in saline-iodine preparations. A combination of the flotation and stained slides gave us a positive result in 99 per cent of the Endamoeba histolytica cases.

In the second series of experiments a similar study of methods was carried out on proctosigmoidoscopic specimens with the following deviations: Quentzel's stain was not used and Balamuth's media (13) was substituted for that of Dobell and Laidlow. Table 2 shows the results of this investigation carried out on specimens from 428 patients with chronic diarrhea. Of this number 76 or 17.7 per cent were found to harbor Endamoeba histolytica. Due to the large amount of cellular material present, especially in cases of ulcerative colitis, the hematoxylin stained slides proved most efficient, permitting a diagnosis in 91 per cent of the positive cases, while zinc flotation yielded 81 per cent of the diagnoses.

TABLE 3.

STOOLS vs. PROCTOSIGMOIDOSCOPIC SPECIMENS FROM 207 PATIENTS WITH CHRONIC DIARRHEA OF WHOM 47 OR 22.7 PER CENT WERE POSITIVE

Specimens (+) and (—)	*# of stools positive per patient*	*PS. specimen*	*# of positive patients*	*% of total positive patients*	*Total % of the positive patients*
Stools (+); PS (+)	3	+	24	51.2	72.3
	2	+	7	14.8	
	1	+	3	6.3	
Stools (—); PS (+)	0	+	6	12.8	12.8
Stools (+); PS (—)	3	—	4	8.5	14.9
	2	—	2	4.3	
	1	—	1	2.1	

PS = Proctosigmoidoscopic.

The first two studies led naturally to the question as to the reliability of methods of collecting material for investigation. As a result an inquiry was made into the advantages of examining spontaneously evacuated stool specimens alone or proctosigmoidoscopic material alone. Three spontaneously evacuated stools collected in approximately weekly intervals and one proctosigmoidoscopic specimen were examined from each of 207 patients with chronic diarrhea. The hematoxylin stained slides and zinc flotation which had proved most effective in the two previous series of examinations were used to detect the amebas. Table 3 demonstrates how many of the 22.7 per cent of amebiasis cases were positive using the aforementioned collecting methods. In 72.3 per cent of the Endamoeba histolytica infections both stools and proctosigmoidoscopic specimens were positive, while in 12.8 per cent the proctosigmoidoscopic specimens alone, and 14.9 per cent the stools alone were found to harbor Endamoeba histolytica. The results proved that in the hands of the authors, the proctosigmoidoscopic method of collecting material for protozoologic study was a most valuable addition to examination of freshly evacuated consecutive stool specimens.

Further investigation into methods of collecting fecal specimens dealt with the importance of the time lapse between collection of the stools and their laboratory examination. As a routine procedure the specimens were always examined, placed in a fixative, and inoculated into media within thirty minutes after collection. As this is not always feasible, particularly in the laboratory where no parasitologist is assigned to the handling of stools, studies were initiated to ascertain what happens to E. histolytica in fecal specimens maintained at incubator, room, or refrigerator temperatures. Fifteen stools which were found to harbor E. histolytica were picked out at random and portions of them kept at 37°, 18° to 20° and 4° C. Samples were examined at ½, 1, 2, 4, 6, 8, 18 and 24 hours for E. histolytica. Table 4 shows the results of this inquiry, demonstrating the individual variations in the survival time of the different strains. Thus the only reliable means for the detection of all strains of this protozoon is the examination of specimens within thirty minutes after stool collection. It was decided, therefore, to adhere to this method in all studies presented here which did not deal with preserved specimens.

In those instances when shipping of the fecal specimens is a necessity, the special problem of preserving the parasites for longer periods of time is encountered. Ten per cent formalin, D'Antoni's iodine (first used as a preservative by McMullen and Gray (13)), Schaudinn's fluid without heating, the polyvinyl alcohol-fixative (14,15) Bouin's fluid, Carnoy's fixative and

TABLE 4.

SURVIVAL OF E. HISTOLYTICA IN STOOL SPECIMENS AT DIFFERENT TEMPERATURES

	Survival time when preserved in or at:—		
Stool # *	Incubator 37°	Room temperature	Refrigerator 4°
1. Trophozoites +++	4 hrs.	1 hr.	1 hr.
2. Cysts +++	2 hrs.	2 hrs.	6 hrs.
3. Trophozoites ++	1 hr.	1 hr.	4 hrs.
4. Cysts ++	1 hr.	2 hrs.	18 hrs.
5. Trophozoites ++	2 hrs.	30 min.	1 hr.
6. Troph. & cysts +++	6 hrs.	1 hr.	1 hr.
7. Troph. & cysts +++	1 hr.	30 min.	8 hrs.
8. Troph. & cysts +++	30 min.	30 min.	30 min.
9. Troph. & cysts ++	30 min.	30 min	2 hrs.
10. Troph. & cysts +	4 hrs.	1 hr.	6 hrs.
11. Trophozoites +	30 min.	30 min.	2 hrs.
12. Trophozoites +	4 hrs.	1 hr.	1 hr.
13. Cysts +	24 hrs.	4 hrs	30 min.
14. Cysts +	18 hrs.	2 hrs.	2 hrs.
15. Cysts +	30 min.	1 hr.	24 hrs.

* = If diluted with saline 1:1, number of protozoa:

+++ one or more per H. P. F.
++ one to each 2 to 5 H. P. F.-s
+ one in fewer than 5 H. P. F.-s

TABLE 5.

EFFICACY OF PRESERVING FLUIDS FOR ENDAMOEBA HISTOLYTICA IN STOOLS

	PRESERVING FLUID:						
Use	*10% formol*	*Faust iodine*	*Schaudinn (cold)*	*P.V.A.*	*Bouin*	*Carnoy*	*Deep freeze*
Trophozoites are kept alive	0	0	0	0	0	0	++
Trophozoites may be stained with hematoxylin	++	0	++++	++++	++++	++++	++++
Cysts may be stained with hematoxylin	++	0	++++	++	++++	++++	++
Cysts may be concentrated with Zn sulf.	++++	+++	+	+	0	0	+++
Protozoa do not suffer shrinkage if examined in	6 days	1 wk.	3 days	6 mos.	1 day	2 hrs.	very individual

P. V. A. = polyvinyl alcohol fixative.

the deep freeze methods of preservation were all given an extensive trial. Because of this experience, the authors present in Table 5 results based on general observations rather than data supported by exact measurements. Schaudinn's fluid and polyvinyl alcohol-fixative are best preservatives for cytologic examination and shipment of specimens. If concentration of cysts by the zinc sulfate method is to be carried out, either formalin or D'Antoni's iodine is preferable. Deep freeze often keeps E. histolytica alive. The effect of temperatures below 25° C., however, varies considerably with the individual strains. Combinations of preservatives may prove very helpful, especially for proctosigmoidoscopic specimens where the hematoxylin stained slide is a "must," and for surveys. For the latter, which frequently have to be shipped for long distances, three small containers are prepared. One of them contains polyvinyl alcohol-fixative from which hematoxylin stained slides are prepared; the second fixative contains D'Antoni's iodine or 10 per cent formalin for direct microscopic examination and flotation; the third holds buffered glycerol-saline for the detection of Salmonellae and Shigellae. Tetrathionate broth, eosin-methylene blue agar, and S. S. plates are inoculated from the latter. This three tube method permits the simul-

TABLE 6.

"TAKES" IN CULTURE MEDIA WITH E. HISTOLYTICA

No. of amebas	No. of takes / No. of tubes inoculated			
in inoculum (1 ml.)	Boeck-Drbohlav	Dobell-Laidlow	Balamuth	Nelson
5 to 10	30/100	32/100	39/100	41/100
15 to 25	47/100	45/100	59/100	55/100
50 to 75	65/100	61/100	67/100	71/100
100 to 200	96/100	97/100	98/100	98/100

10 trials with each medium, using 10 tubes at one time.

TABLE 7.

MICROSCOPIC EXAMINATION OF STOOL SPECIMENS

E. histolytica	Salm. or Shig.	Age of Pts.	No. of Exam.	Ch-L cryst.	Excess fat	Mucus	Percent of elements harbored in patient's stools: RBC's	WBC's	Macrophages	Slough. epithel.	Many molds + yeasts	Blasto. hominis
Present	Not grown	Ad	302	11.6	49.0	44.3	10.2	55.9	39.8	31.4	62.6	26.5
		Ch	74	17.6	35.1	56.8	8.1	44.6	41.9	31.1	50.0	23.0
	Salm.+	Ad	19	15.8	47.4	31.6	10.5	52.6	52.6	31.6	78.9	31.6
	Shig.+	Ad	17	5.9	47.1	35.3	17.6	76.5	82.4	35.3	70.6	23.5
Not found	Not grown	Ad	67	11.9	43.2	41.7	5.9	47.7	34.0	41.7	58.2	20.8
		Ch	35		40.0	45.7	2.9	28.5	45.7	57.1	57.1	5.7
	Salm.+	Ad	50	2.0	16.0	54.0	10.0	46.0	44.0	14.0	28.0	30.0
		Ch	35		22.8	51.3	8.2	42.8	42.8	22.8	31.4	20.0
	Shig.+	Ad	35	17.1	17.1	65.3	65.3	77.1	71.4	40.0	31.4	36.7
		Ch	50		4.0	80.0	36.0	56.0	70.0	28.0	34.0	10.0

Salm. = Salmonella
Shig. = Shigella
Ch-L cryst = Charcot-Leyden crystals
pts. = patients
Slough. epithel. = sloughing epithelial cells

taneous examination for protozoa, helminths, Salmonellae and Shigellae.

The results in our second series of experiments demonstrating the relative inferiority of cultures as a diagnostic means in amebiasis, bore out our experience as well as that of other parasitologists (16). Amebas do not parallel bacteria in the regularity with which they develop in artificial media and the change in morphology of E. histolytica during cultivation may be considerable. In the next study an attempt was made to demonstrate the number of E. histolytica which must be present in a stool specimen before a successful culture can be made. The media of Boeck and Drbohlav, Laidlow, Balamuth and Nelson were used. Trials with ten specimens were carried out on each medium using ten tubes at one time, with undiluted specimens less than thirty minutes old. Counting of the amebas was performed using the dilution method (17). Table 6 shows the dependency of diagnostic amebic cultures on the number of organisms present in the stools. The 95 per cent fiducial limit of probability of diagnosing amebiasis is reached only when more than 75 amebas are present per gram of stool. This is a rather heavy inoculum when compared to the 0.1 to 0.2 grams used to prepare two hematoxylin stained slides. Taking into account only the lower limit and using the Poisson distribution (because of the small number of organisms present), 3.41 amebas should be detected in 0.1 gram of stool, (or about 34 in 1 gram of stool) in 95 per cent of the positive cases if two slides are prepared and carefully examined. This is considerably superior to the culture method which requires more than 75 amebas per gram of stool to achieve the same result.

TABLE 8.
RESULTS OF SURVEYS FOR E. HISTOLYTICA IN PERSONS FROM COOK COUNTY
1942-1949

Persons examined	Method used	No. positive	%
237 medical students	Saline-iodine, Hematoxylin-slides, 2 specimens	10	4.2
796 food handlers	Saline-iodine, Zn flotation, 3 specimens	93	11.6
349 cases of bacillary dysentery in State Hospitals	Saline-iodine, Zn flotation, one specimen	15	4.3
428 cases with chronic diarrhea, State Hospitals	Saline-iodine, culture, Hm slides, Zn flotation, one specimen	76	17.7
207 cases with chronic diarrhea, clinic for poor patients	Hm slides, Zn flotation, 3 stools + one proctosigmoid spec.	47	22.7
1587 cases with chronic diarrhea, County Hospital	Saline-iodine, Hm slides, Zn flotation, average 4 stools	309	19.4
617 adults with chronic diarrhea, private hospital	Saline-iodine, Quentzel, Hm slides, culture, Zn flotation, one specimen	103	16.7
196 children with chronic diarrhea, private hospital	Hm slides, Zn flotation, 3 specimens	6	3.1
121 physicians with chronic diarrhea, overseas service	Hm slides, Zn flotation, 3 specimens	37	30.6
5,048	13,333	696	

Hm = hematoxylin stained.

The examination of stools for elements other than parasitic forms, Salmonellae or Shigellae, was always carried out by the authors in the belief that it may prove helpful in establishing the etiology of the disease. The question arose, however, if the microscopic picture might be different in the "low grade" amebiasis which constitutes the vast majority of cases observed in northern Illinois. To add further complications, frequently sequelae such as "chronic irritable colon," "mucous colitis" and "non-specific ulcerative colitis" may have developed before parasitologic stool examinations were undertaken. Table 7 shows the results of complete microscopic stool studies in 302 adults and 74 children with intestinal amebiasis only, and 36 adults harboring E. histolytica together with Salmonellae or Shigellae. This is compared with 272 cases in which E. histolytica was not found of whom 67 were adults and 35 children suffering from chronic intestinal disturbances with no etiologic agent discovered, and 85 were adults and 85 children with acute intestinal Shigellosis or Salmonellosis. It is known that Charcot-Leyden crystals may occur in a number of conditions other than amebiasis, of which the intestinal allergies are here most frequent. On the other hand, sensitization to food, especially to milk and eggs, is by no means a rare phenomenon in amebiasis (18) and other ulcerative conditions. Table 7 shows that Charcot-Leyden crystals were present in many non-amebic cases. Yeasts and molds were especially numerous in chronic conditions. Excess fat seemed also to be more indicative of a chronic condition. Mucus, as well as pus cells, macrophages and sloughing epithelial cells were found on careful examination to be present in many disturbances. Red blood cells, as was expected, were most often seen in acute shigellosis. It was concluded that the examination of stools for elements other than pathogenic microorganisms, while very helpful in the guidance of symptomatic and local treatment, was of little help in recognizing chronic, low-grade amebiasis.

As a final study, the relative frequency of amebiasis in different groups in Chicago and Cook County is presented in Table 8. Some of these data were published previously (19,20,21,22,23) and some are unpublished. They were put together and presented with the technics used for each group to give as complete a picture as possible. The first two groups shown in Table 8, including medical students and food handlers, represent, as far as could be determined, symptomless persons. 4.2 per cent of the former group and 11.6 per cent of the latter were found to be positive for E. histolytica. The number of students harboring this protozoan would be higher if zinc flotation had been employed for the examination of their stools. The second group of specimens examined represents a study of amebic infections in mental hospitals. Conditions within the hospitals made it impossible to carry out repeated examinations on one patient, so the percentage shown is undoubtedly low. The results also seem to indicate that E. histolytica disappears from the feces

of many persons afflicted with acute shigellosis or salmonellosis. Groups 3 and 4 represent findings from cases of chronic diarrhea among poor and better situated patients, respectively. When the number of specimens examined and the technics employed are considered, the differences in percentage of cases between the two groups is not as great as might be expected. The last group studied were physicians after overseas service, who were suffering from chronic diarrhea. A high proportion (30.6 per cent) had an amebic infection.

SUMMARY

The paper presents a complication of extensive studies made on methods used for the detection of Endamoeba histolytica, and the application of those methods to the examination of more than 13,000 fecal specimens from 5,048 persons during the past 7 years in Chicago and Cook County, Illinois. Combined fecal and proctosigmoidoscopic specimens examined within 30 minutes after collection, employing hematoxylin-stained slides and zinc sulfate flotation, gave optimal results. The irregular behavior of E. histolytica at different temperatures is presented, necessitating their preservation if examination is not carried out within 30 minutes. Advantages of polyvinyl alcohol and Schaudinn's fixative for hematoxylin stained slides and those of formalin and D'Antoni's iodine for flotation were pointed out. Results of stool examinations for other components than parasites and bacteria were compiled and their lack of value for etiological, but usefulness in guidance of symptomatic treatment were shown. The approximate proportion of E. histolytica infestations in patients suffering from chronic intestinal disturbances in the Chicago area is estimated as 20 ± 3 per cent.

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THE SURGICAL TREATMENT OF REGIONAL ENTERITIS

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NOWHERE IN THE VOLUMINOUS literature that has appeared on the subject of regional enteritis since the definition of the disease as a pathologic entity by Crohn, Ginzburg and Oppenheimer in 1932 (1) can there be found agreement as to the most successful method of treatment in those cases where surgery is indicated. Despite the note of pessimism sounded in many reports because of the high rate of recurrence of the disease only a few authors such as Cutler (2) have come out squarely against surgery as a form of therapy for this condition. It is now assumed by the majority that in the chronic stage of the disease, particularly where intestinal obstruction or fistula formation is present, that surgery is the treatment of choice. The bone of contention is the type of operative procedure which should be carried out.

Since the greatest number of cases recognized for the first time as regional enteritis appear in an acute exacerbation of the chronic form, it must be recognized that the principal therapeutic approach is now surgical, and that other measures are employed only to prepare the patient for surgery or for palliation of the inoperable or hopeless patient.

HISTORY OF SURGICAL TREATMENT

In his monograph entitled "Regional Ileitis," Crohn (3) discusses the historical development of surgical

treatment for this disease and attitudes arising from the results obtained. He points out that resection in one stage was the initial procedure of choice. To this period belong the reports of Meyer and Rosi (4) in 1936, Koster, Kasman and Sheinfeld (5) in 1936, Mixter and Starr (6) in 1938, Clark and Dixon (7) in 1939, and Shapiro (8) in 1939. These authors find in their own or in collected series of cases a great predominance of resected cases. It is instructive to examine these reports in a little detail in the light of subsequent events.

Meyer (4) reported on 8 cases, of which 7 involved the ileum alone and 1 the jejunum. Three patients had appendectomies and were well for 1 year. Five patients were subjected to one-stage resections, and 4 were well from 1 to 4 years. Koster (5) reported 17 cases on which he had operated. Seven were treated by one-stage resection with no deaths and no recurrences. Four of these patients had been followed over 2 years. Three were treated by two-stage resection with one death. The remainder had appendectomies with no mortality. He also reported on 100 cases out of 126 collected from the literature where the type of surgery and the result were clearly recorded. The general mortality of the bigger series was 14 per cent. There were 65 resections with 10 recurrences, a rate of 15 per cent. In 6 cases a second operation was successful and in 3, death resulted. There were 15 side-tracking procedures with 1 recurrence and 1 death. Fourteen cases were explored and 8 of these were well. The remaining 6 were later resected with 4 cures, 1 recurrence and 1 death.

Mixter (6) reported 19 cases operated on with 4 appendectomies and no mortalities, 8 one-stage ileocecal resections and one death (13 per cent), and 7 multiple-stage procedures with 3 deaths (43 per cent). The resected cases were followed from 6 months to 6 years with only one recurrence, which took place after 8 months. Clark (7) cites 44 cases operated on with a total mortality of 11.5 per cent. Twenty-seven of these patients had been previously operated upon including 6 with ileocolostomies and 4 with resections. Among 14 ileocolostomies performed by the authors there were 4 postoperative deaths with 5 patients later well and 5 unimproved. Exclusion of the terminal ileum was carried out in only three. Among 14 wide one-stage resections there were no postoperative deaths and 12 patients were well up to two years later. Among 15 two-stage resections there was one postoperative death and 12 patients were well also up to two years later.

Shapiro (8) in a review of 448 surgical procedures collected from the literature up to 1939, found 290 resections with a mortality of only 7.2 per cent and 68 per cent of the patients listed as completely recovered. The recurrence rate was only 10 per cent, counting those in which there was no improvement. He found 88 short-circuiting procedures with a mortality of 8 per cent, only 30 per cent complete recoveries and 34 per cent recurrences. There were 70 appendectomies in acute cases with 56 per cent recoveries, 20 per cent recurrence and 4 per cent operative mortality.

Resection had been strongly advocated by Ginzburg and Oppenheimer (9) who stated in 1933 that, while a short-circuiting procedure might cause the acute process to subside, the disease remained active in the terminal ileum, and that acute peritonitis with perforation and a fatal outcome might occur. Clark and Dixon (7) showed in a small series that the mortality and rate of recurrence were high in cases treated by short-circuiting alone.

Gradually there began to appear more reports in which two-stage resections predominated. This second phase of the attack was led by the Lahey Clinic group, whose figures were published by Marshall (10, 11), and by the Mayo Clinic, whose results have been reported variously by Brown and Donald (12), Mayo and Judd (13), and Pemberton and Brown (14). A third paper by Mixter (15) reviewed the experience of many different surgeons. In general this tendency represented a reaction to what was considered an excessively high mortality rate for the one-stage procedure. It also reflected the fact that many of the cases coming to these centers had recurrence of disease following a previous operation elsewhere. A brief consideration of the results is pertinent to later discussion.

Marshall (11) reported on a series of 55 patients who had operations with a gross mortality of 5.5 per cent. Thirty-nine of these patients had a two-stage resection, of which 34 were of the Mikulicz variety with one death. Seven patients had a primary resection and anastomosis without mortality, and five ileostomy only with one death. Follow-up data were obtained on 42 patients in this series over periods of one to five years. There were only five recurrences, a rate of 9.6 per cent. It is not specified in which group of operations the recurrences were found. The Mikulicz operation, however, is only a slightly modified one-stage procedure since the resection is almost entirely carried out in the first stage.

Mayo (13), summarizing the work of the Mayo group, listed 100 resections for non-specific ileocolitis. Of these, 32 were performed in one stage with a mortality of 22 per cent, and 64 in two stages with a mortality of 3 per cent. The average interval between the first and second stages was 14 months. Four patients had more than one-stage procedures, and one died. Following the one-stage resection, 24 patients were followed from one to five years. Thirteen were cured, seven improved, two had recurrences of whom one died, and two more died later at home. The percentage of poor results was 16 per cent. Fifty-seven patients were followed one to five years after the two-stage resection. Of these, 26 were cured, 18 improved, nine worse and three died. This indicates a failure rate of 21 per cent.

Mixter (15) sent out a questionnaire designed to evaluate the results obtained by various forms of treatment to those individuals and clinics where he thought the widest experience with this disease had been obtained. He received replies from 31 individuals and clinics concerning 363 cases of regional enteritis. These indicated that 278 major surgical procedures had been performed in this group with a mortality of 14 per cent. There was a 20 per cent recurrence rate for all operative cases in follow-up periods varying from six months to six years, the majority having been followed more than one year.

Twenty-five out of 27 surgeons responding favored radical resection as the treatment of choice. The author declared himself in favor of this method, preferring multiple-stage procedures where possible.

At the same time a third type of surgical approach came into prominence, chiefly through the very strong recommendations made for it by the group of surgeons from the Mt. Sinai Hospital in New York. This was the ileocolostomy with transection of the ileum above the site of disease so that exclusion of the involved area from the passage of the fecal stream was accomplished. The principal papers of importance in influencing this trend were those by Lewisohn (16), Ginzburg, Colp and Sussman (17), Colp and Ginzburg (18), Ginzburg and Garlock (19), Garlock and Crohn (20), and finally, in 1949, the monograph by Crohn (3). The evidence presented is impressive and should be carefully reviewed.

Lewisohn (16) in reporting nine cases of short-circuiting or two-stage procedures cautioned that transection of the ileum above the location of the disease was essential to cure. It was his opinion that the bowel would heal itself if put at rest. Colp and Ginzbug (18) presented 22 cases of ileocolostomy with transection, a further report on the 14 cases previously published with Sussman (17). There were only three recurrences during the follow-up period, a rate of 14 per cent. Four patients were subjected to reoperation because of persistence of diarrhea, and in each instance the original site of disease in the ileum appeared to be completely healed. There were no surgical deaths. The series was extended to include 54 cases treated in this manner in the report of Ginzburg and Garlock (19), and finally, 65 cases in the paper of Garlock and Crohn (20). There was still no surgical mortality for this type of procedure, and only 14 per cent recurrences. Persistence of the disease in the excluded loop was noted in five cases. Three of these patients were resected and were well. The remaining two died without a second operation. This was contrasted in the final paper with 55 one-stage resections accompanied by nine deaths (16 per cent) and nine recurrences (20 per cent), and 25 two-stage resections accompanied by three deaths (12 per cent) and eight recurrences (36 per cent), all performed at the same hospital. The follow-up period varied from two to 14 years.

Crohn (3) divides those of his 222 cases which have been subjected to surgical treatment into four groups: chronic regional ileitis, acute ileitis, ileojejunitis, and ileocolitis. There were 108 cases in the first group, including 57 treated by ileocolostomy with transection, 36 treated by primary resection and ten by two-stage resection. In the whole group there were 28 postoperative recurrences of which 14 occurred within one year, but two occurred after 12 and 16 years. There were 16 cases in the second group of acute ileitis, of which four were not operated upon and two are well. There were no primary short-circuiting procedures in this group. In the third group of 38 cases of ileojejunitis there were less than five short-circuiting procedures and the results are not given separately. In the last group of 22 cases of ileocolitis there were only four ileocolostomies with transection. One patient is well and there are three recurrences.

Throughout the development of these three phases of the surgical attack on regional enteritis there have also been isolated papers by individuals or groups reporting small numbers of cases. There are many reports of single cases with varied treatment which it would serve no purpose to list here. There are several papers worthy of mention, however, which demonstrate what confusion exists in determining the indications for the different types of surgical procedures.

Sneiersen and Ryan (21) report on 22 cases which they have treated in a small general hospital. Eight were explored without resection and all recovered and were well up to four years later. Fourteen had radical resections with a total mortality of 21 per cent. There were no deaths in the four cases who had Mikulicz or two-stage resection. There were four recurrences in the surviving cases. Eckel and Ogilvie (22) discuss 21 patients in whom 24 operations were performed without immediate mortality. There were two simple explorations, 11 appendectomies, six resections in the ileum only, two one-stage resections, two two-stage resections and one secondary enterostomy. One of those explored only, two of the appendectomies, and two of the resections in the ileum did poorly and the secondary enterostomy died six months later. The periods of follow-up were not given. Svec and Mahle (23) presented nine cases treated by various surgical methods of whom four were well three to five years and the remainder lost to follow-up or too recent to evaluate. Blackburn (24) reports 22 cases treated by the three different surgical procedures with follow-ups of one to four years. The majority were treated by one-stage resection and all are considered to be cured.

Fallis (25) lists 28 radical resections with an operative mortality of 3.6 per cent. Seven were done for recurrence following previous resections by other surgeons. Two side-tracking procedures were done; one died in the hospital and the other at home a year later. Follow-up on the resected cases is not given. Halloway (26) discusses 13 operative cases. There were five appendectomies followed for an average of five years without recurrence. Six resections were followed for an average of six years with two poor results, one after six and the other after eight years. The only lateral anastomosis had to have a resection after two years. Rossmiller (27, 28) treated 55 patients surgically. Forty-seven survived the postoperative period, an overall mortality rate of 15 per cent. Forty of these were followed from one to 15 years. Twenty-one patients had side-tracking procedures of which all but two were without transection of the ileum. One of these died as did five others, and the other did poorly, as did nine others of the 12 that were followed. Thirty-five patients had resections, of which 15 were in two stages with no mortality in this group. Only two patients had a satisfactory result following a one-stage resection. Six died and three were not followed. Seven had a subsequent resection and five were improved. Thirty-one patients were followed altogether of which 23 had a satisfactory result, a recurrence rate of 26 per cent.

Finally there is a group of reports, including two of recent origin, that express disillusionment with results of all types of surgical treatment. Cutler (2)

presented the results of 11 cases operated on at the Peter Bent Brigham hospital. There were two in which exploration only was carried out of whom one was alive nine years and the other eight months and both fairly well. There was one appendectomy with a good follow-up report after six months. There were eight resections with one death, a mortality of 12.5 per cent. Five of these patients were well but still had some symptoms, notably diarrhea. Two had no evidence of disease. He drew the rather surprising conclusion that surgery should be performed only for obstruction or fistula and in those cases, a permanent ileostomy should be made. Felger and Schenk (29) reported 13 cases of recurrence of the disease collected from the literature and including two of their own. The time of recurrence varied up to nine years. Two cases represented second recurrences in the same patient.

Warren and Miller (30) report 26 cases in which resections were done, and five in which side-tracking only was carried out. There was only one postoperative death, a gross mortality of only 4 per cent. Nevertheless only six patients were symptom-free on follow-up and only two more were not so sick as to be incapacitated. In the five patients with side-tracking procedures, the ileum was transected in four and yet only one recovered; the patient whose ileum was not transected also recovered. In 16 one-stage resections, only two recovered and two later died of the disease. In ten two-stage resections, four recovered and one later died. Twelve cases seen by these authors were treated without surgery, of which five recovered and two later died. The recurrence rate in this series following surgery is therefore 69 per cent. Starr (31) cites a recurrence after 15 years. He does not think resection of the involved mesenteric lymph nodes is necessary. He points out the severe psychic disturbances which seem to accompany many of these cases and suggests that this may be a psychosomatic rather than a surgical problem. Hawthorne and Frobese (32) report 24 radical resections with only two operative deaths (8.3 per cent). Seven patients were followed less than one year. Fifteen were followed from one to 14 years and there were recurrences in 11 (73 per cent). They have now done six short-circuiting procedures with four patients symptom-free after only two years.

REPORT OF CASES

Six cases operated upon at the Meriden Hospital between 1928 and 1945 are presented. These were winnowed from a larger group in which the diagnosis had been made on the record but where sufficient clinical or histological evidence of regional enteritis was lacking, or where, as in two cases, the diagnosis of tuberculous enteritis was finally demonstrated. There may have been other cases since 1932 in which the diagnosis was suspected or made in retrospect but does not appear as the final one on the chart. To these six cases are added two personal ones.

Case 1. A 24 year old white male was admitted on October 25, 1928 with a complaint of peri-umbilical pain for two weeks. He had a similar previous attack two years before. On physical examination he appeared acutely ill. His temperature was 100.0° and his pulse 92. Tenderness was present around the umbilicus and there an ill-defined abdominal mass was felt. The white blood count was 9,400 with 64 per cent polymorphonuclears. Operation the same day revealed a typical appearance of regional enteritis localized to the region of the ileocecal valve. Appendectomy was carried out and the histological examination showed a normal appendix.

The patient made a good immediate recovery but returned to the hospital on January 27, 1929 complaining of recurrent abdominal pains since shortly after the first operation. This time he did not appear acutely ill but his temperature was again 100.0° and his pulse 88. There was diffuse abdominal tenderness and a mass in the right lower quadrant. The impression was of intestinal obstruction. At operation more extensive involvement of the terminal ileum and apparently of the cecum was seen. A one-stage resection of four inches of cecum and eight inches of terminal ileum was carried out.

The patient again made a good immediate recovery but had a recurrence 1½ years after the second operation. A colostomy was performed at another hospital for symptoms of obstruction. Attempts to close this subsequently were unsuccessful and a fistula developed. There were repeated admissions at this and other hospitals for abdominal pain, vomiting and diarrhea. X-ray examination showed chronic obstruction in the ileum. The patient finally died of his disease on November 18, 1949.

Case 2. A 38 year old white man was admitted September 11, 1935 because of cramping abdominal pains for nine months. There had been no vomiting, diarrhea or weight loss. Physical examination showed a well-nourished young white male who did not appear acutely ill. His temperature was 99.0° and pulse 72. The abdomen was distended and a mass was palpated directly beneath McBurney's point. At operation a typical appearance of regional enteritis was seen involving the terminal ileum and apparently the cecum. A Mikulicz resection in one stage was carried out, removing the terminal ileum, cecum and part of the ascending colon. The patient died five days postoperatively. No post-mortem examination was obtained.

Case 3. A 45 year old white male was admitted March 28, 1936 because of acute lower abdominal pain for one week accompanied by vomiting. For the previous six months he had experienced chronic indigestion and weight loss. The diagnosis of acute appendicitis had been made before admission and operation at first refused. Physical examination showed an emaciated middle-aged man appearing chronically ill. His temperature was 100.0° and his pulse 90. Hemoglobin was 80 per cent and the white blood count 11,800 with 82 per cent polymorphonuclears. At operation a typical appearance of regional enteritis was found involving the terminal ileum and apparently the cecum. A Mikulicz resection of the terminal ileum and cecum was carried out in two stages. The patient died three days postoperatively. Postmortem examination showed gangrene in the terminal ileum.

Case 4. A 52 year old white male was admitted January 18, 1942 because of acute abdominal pain for 12 hours. There was no vomiting or diarrhea. On physical examination he appeared acutely ill. His temperature was 99.4° and pulse 80. The abdominal examination showed tenderness in the right lower quadrant but no mass was palpable. Hemoglobin was 80 per cent and the white blood count was 12,600 with 86 per cent polymorphonuclears. At operation an acute inflammatory process, typical of the acute stage of terminal ileitis, was found. The appendix was removed and hirtologic section showed it to be normal. The patient made a good immediate recovery from the operation. The patient died at home in 1944, presumably of cancer. It is not known whether he had any further recurrence of symptoms, which could be attributed to his acute ileitis.

Case 5. A 4 year old white boy was admitted March 16, 1943 because of acute abdominal pain for 18 hours with vomiting but no diarrhea. The child appeared pale and acutely ill. His temperature was 99.6° and his pulse 82. There was spasm and tenderness in the right lower quadrant of the abdomen but no mass was palpated. Hemoglobin was 61 per cent and white blood count 9,900 with 83 per cent polymorphonuclears. At operation acute terminal ileitis was found and the appendix was removed. A large lymph node was removed for biopsy. Histologic examination showed a normal appendix and non-specific inflammatory reaction in the lymph node. The boy made a good immediate recovery from the operation. Seven years later the child is reported to be

well and has had no symptoms of recurrence since the operation.

Case 6. A 21 year old married white female was admitted June 1, 1945 with a complaint of pain in the right side for eleven days. Fever and vomiting had occurred on the night before admission. There was no diarrhea. Her temperature was 102.4° and her pulse 110. There was spasm and tenderness in the right lower quadrant of the abdomen but no mass was felt. On pelvic examination there was tenderness on the right side and a feeling of a mass. There was some vaginal discharge. Hemoglobin was 60 per cent and the white blood count was 32,000 with 91 per cent polymorphonuclears. A diagnosis of appendicitis or tuboovarian abscess was made. At operation dark red fluid was found in the peritoneal cavity. The mesentery of the ileum contained many enlarged lymph nodes. The principal mass, which was about four inches in diameter, appeared to involve the cecum primarily in the region of the ileocecal valve. A Mikulicz resection of the terminal 12 inches of ileum, cecum, ascending colon and right half of the transverse colon was performed in two stages on successive days. Examination of the specimen removed in operation showed a typical appearance of regional enteritis with edema of the terminal ileum, cecum and appendix and the presence of a small abscess in the mesentery near the ileocecal junction. The patient made a good recovery from operation and was discharged after two weeks, only to be readmitted in six days with cramping abdominal pain but no vomiting or diarrhea. She was discharged after three days of conservative management. Since then she has carried through a normal pregnancy and is, at the present writing, free of symptoms.

Case 7. A 25 year old white male was admitted to the hospital August 15, 1945 because of recurrent crampy abdominal pains, vomiting and diarrhea. Abdominal drainage for peritonitis followed by appendectomy later had been performed three years previously and no evidence of regional ileitis noted. The patient complained that he had been unable to maintain his weight because for many months the taking of any food caused cramping abdominal pain and diarrhea. On physical examination he appeared younger than his stated age and generally underdeveloped, although of average stature. He was acutely and chronically ill. The abdomen was distended and tympanitic. There was a right lower rectus incision. Peristalsis was high-pitched and hyperactive. An ill-defined mass could be made out in the right lower quadrant. Tenderness was diffuse throughout the abdomen. Hemoglobin was 60 per cent and the white blood count 18,000 with 82 per cent polymorphonuclears. The total serum protein was 5.8 gm. per cent.

Plain x-ray examination of the abdomen and with barium through a Miller-Abbott tube passed down into the ileum demonstrated the extreme narrowing of the terminal ileum characteristic of terminal ileitis. The patient was kept on intestinal suction and prepared for operation with blood transfusion and sulfasuxidine.

At operation on August 25, 1945 a shaggy-looking loop of small bowel was seen lying adjacent to the cecum in the position occupied in the x-ray studies of the small bowel by a doughnut-shaped loop of barium. This bowel was almost covered by an overgrowth of fat from the mesentery which had a rainbow-colored appearance. The mesentery itself was greatly thickened and quite friable, and it contained many enlarged lymph nodes. The cecum was scarred, thickened and fairly well fixed to the posterior abdominal wall. The terminal ileum was involved in a similar process extending eight inches from the ileocecal junction. It was extremely narrow and did not manifest any active peristalsis. Between this terminal ileum and the portion first seen when the abdomen was opened was a distance of approximately three feet. In this space there were three portions of bowel varying in length from four to eight inches, which were involved in the same type of pathological process. The remainder of the small bowel was explored and was apparently uninvolved. Because of the extensive involvement of the ileum with skip areas and the extreme fixation of terminal ileum and cecum, it was decided to do a by-passing procedure rather than a resection. The ileum was transected six inches proximal to the highest involved area. A side-to-side anastomosis was performed between the ileum and the transverse colon.

The patient made a good recovery from the operation but continued to have four to five watery bowel movements daily. He gained some weight and was eventually able to return to work with only one episode of diarrhea weekly. He was readmitted to the hospital September 5, 1946 because of fever, abdominal pain and diarrhea for 36 hours. On physical examination the patient appeared acutely ill. His abdomen was slightly distended and there was minimal tenderness in both upper quadrants. There was acute tenderness in both lower quadrants. In the right lower quadrant a tender, movable, lobulated, cylindrical mass, 10 cm. in diameter, was palpated. Hemoglobin was 15.5 gm. and the white blood count 18,500 with 87 per cent polymorphonuclears. The patient was started on sulfasuxidine and penicillin. Within 24 hours the mass had almost disappeared and the abdomen was soft and non-tender. Barium studies of the colon and small bowel showed the presence of the anastomosis between what appeared to be lower jejunum and the transverse colon but no obstruction. The patient was discharged in 12 days as recovered.

Subsequently the patient was treated for a year and a half as an outpatient in the psychiatric clinic of the hospital. His chief complaint was diarrhea. He was unable to maintain his weight in spite of a good appetite. Because of weakness and of the necessity of moving his bowels frequently, he was unable to hold a job. X-rays of the small intestine and colon in 1947 and 1949 revealed no evidence of recurrence except for some irritability of the small bowel near the stoma. The following quotations from letters written to the author by the patient this year are indicative of the troubled mental state which is so characteristic of many of these patients:

"Most of my problem stems from an unhappy home atmosphere. . . . I have been living in a home where dissention, suspicion and envy have existed for a long time. I have always been in the middle and I guess a person who was very healthy could eventually develop some ailment like ulcers. I have often thought of leaving home and trying to make a go of it. . . . I feel depressed and mostly alone at all times. . . . I hate to burden you with my troubles but it's because I feel alone and have no one to turn to. . . . The most important task is adjusting myself to whatever capacity my physical being can endure. My feelings, emotions are natural and being without social life, a job, self-respect and independence is hard. The days are long and dreary sometimes. . . . It is not necessary for me to explain that medication can do so much for a patient, especially in cases like mine. . . . Where spiritual and emotional factors are present, the medication has far less chance of being potent. So it is in my case. The food I consume has very little chance of doing me any good, if spiritually and emotionally my heart hangs heavy and hard."

On examination in January, 1950, the patient weighed 106 pounds. He did not appear ill. The abdomen was soft with slight to moderate general tenderness. Peristalsis was hypoactive. No mass was palpated. A small hemorrhoid and a scarred anal fistula were seen. Ankle edema was present. The patient was placed on a high-protein, low residue diet, Cellothyl and a combination of phenobarbital and belladonna. His ankle edema has now disappeared but he is still having watery movements.

Case 8. A 16 year old white boy was admitted to the hospital September 28, 1949 because of recurrent crampy abdominal pain for three years. An appendectomy had been performed five years ago and a "chronic appendix" removed. During the last three years the patient had suffered from intermittent diarrhea as well as crampy pain. He ate very little because taking food induced pain and, consequently, did not gain weight. The constant abdominal distress had caused him to avoid the company of other boys his age and to become very seclusive. A recent x-ray examination in another hospital had shown calcification in some mesenteric lymph nodes which led to a diagnosis of intestinal tuberculosis.

The patient appeared as an apprehensive, withdrawn young white male who was undersize and underweight for his age. He was acutely and chronically ill. There was a Battle incision on his abdomen which was moderately distended and tympanitic. It was diffusely tender, more so in the right lower quadrant. No mass could be palpated. On rectal examination, there was no mass or tenderness and no fissure or fistula. Hemoglobin was 77 per cent and the white blood count 29,500 with 98 per cent polymorphonuclears. The total serum protein was 6.62 gm. per cent with 4.52 gm. per cent

albumin and 2.10 gm. per cent globulin. Other blood chemistry was within the normal range.

X-ray examination of the abdomen on admission showed gaseous distention of a few loops of small bowel suggesting early small bowel obstruction. Injection of barium into the terminal ileum after a Miller-Abbott tube was passed showed obstructive changes in the terminal ileum due to narrowing of its lumen with associated involvement of the cecum, probably due to regional enteritis. Sigmoidoscopy showed only a glistening appearance of the mucous membrane and the presence of considerable mucus. The patient was prepared for operation with blood transfusion and with dihydrostreptomycin.

At operation on October 5, 1949, there was a small amount of free fluid in the peritoneal cavity. The distal segment of ileum adjacent to the cecum was distended for a distance of about 1½ feet. The mesentery of the small intestine was filled with enlarged lymph nodes, some of which were as large as 2 cm. in diameter. The mesentery showed the characteristic fatty infiltration and color-play of regional ileitis. Near the ileocecal junction folds of fat extending up over the intestine were seen. The cecum itself was bound down by most dense adhesions to the posterior parietal peritoneum. There appeared to be direct extension of the inflammatory process into the posterior parietal peritoneum at one point. The small intestine was searched for other areas of inflammatory process but none were seen. The terminal 1½ feet of ileum, cecum and ascending colon were resected together with a considerable portion of the posterior parietal peritoneum and the mesentery containing the majority of the enlarged lymph nodes. An end-to-side anastomosis was made between the ileum and the transverse colon. Gross and microscopic examination of the specimen showed that the disease process terminated sharply at the ileocecal valve, although there was edema of the serosa of the cecum, probably due to involvement of its small lymphatics.

The patient made an uneventful postoperative recovery. He was discharged on the twelfth postoperative day eating a modified high protein diet and having normal bowel movements once or twice daily. Since discharge he has returned to school and has gained 40 pounds. At the present time (June 1, 1950) he has no abdominal complaints and is moving his bowels one to three times daily.

DISCUSSION

These eight patients almost represent a microcosm of this disease: the young boy and the middle-aged man with acute terminal ileitis who were treated by appendectomy with no further manifestations; the young man with recurrent pain who has first an appendectomy and then a resection with recurrence followed by poorly planned later operative procedures, a permanent invalidism and then death; two relatively young men with subacute symptoms, relatively localized disease, but dying after resection; a young woman with acute enterocolitis making a good recovery following a two-stage resection and free of recurrence after five years; a young man with recurrent disease following an episode of peritonitis showing extensive disease, cured of obstruction by a side-tracking operation but still chronically disabled by diarrhea; and finally a young man with recurrent symptoms following appendectomy, having localized disease and with an excellent immediate result following resection but an uncertain future. The only things missing are a case of fistula formation, and a case of jejunitis.

The experience with treatment of these cases varies hardly at all from that presented in the typical report of a small series in the literature. The net impression is one of discouragement. It is difficult for any individual or group except those in the large medical centers to find enough cases of this disease so that any plan of surgical management can be adequately evaluated from the local experience. It has also been clearly demonstrated that a long follow-up period is necessary before the results can be judged fairly. Consequently the surgeon must rely upon what he can find out from the literature. How is he to derive a clear guide from the confusing mass of evidence which is now available?

At first, the conception of collecting a number of cases from the expanding literature and dividing them into categories seems attractive. By this method at the present time the reports of close to 1,000 cases could be catalogued, the types of treatment and results noted and perhaps some conclusion drawn as to which management produced the greatest number of cures. There are five objections to this plan of analysis, however. Primarily, the multiphasic nature of the disease, which still remains of unknown etiology, defies accurate comparison of the cases.

Secondly, the possible variations in the surgical approach are so many that it is impossible to compare methods exactly. One man does a wide resection and carefully removes all the involved nodes he can see; the next does a wide resection but disregards the nodes. The complications, particularly fistula, which often ensue following an earlier operative procedure, create a great variance in the scope of subsequent procedures. It has been demonstrated that with careful modern methods of pre- and postoperative management that the mortality, even for resections in extensive cases, can be kept below 5 per cent. This makes a comparison with older series difficult, since patients with more extensive disease are surviving the first surgical attack to become recurrences later on.

Thirdly, the period of follow-up must be a long one if we are to know the eventual result in these patients. Recurrences have been reported as late as 15 years following the primary procedure. In too many of the reports found in the literature the period of follow-up is not mentioned or is too short to be of any significance. This unfortunately applies to some of the largest series. In comparing the side-tracking operation which includes transection of the ileum with the classical two-stage resection, of which the former is the first stage, too many patients are included who represent failures of the first stage operation. Perhaps there are also some whose second-stage is not done because of the amelioration produced by the first stage and who are later recurrences because of this.

This leads to the fourth objection, which is that undoubtedly too many patients are included under different headings in more than one series. If all the duplications could be weeded out, perhaps the total number of cases would be smaller than is now indicated. It has been pointed out by several authors that one man's success may be in a few years another man's failure. As is the case with all patients suffering from chronic debilitating disease, these patients are great "shoppers" and tend to gravitate eventually to the large clinics which are known for their experience in treating these difficult problems.

Fifth, and lastly, is the fact that too much emphasis has been laid upon the techniques of surgical management in these patients to the exclusion of equally important considerations. There is an extremely pressing necessity for physical, mental, social and economic rehabilitation of the great majority of patients with this disease. Certainly there are many things which tend

to support Starr's (31) suggestion that this is a so-called psychosomatic condition. The emotional readjustments necessitated by such a potentially chronic and disabling entity may be severe, if not partially or completely irreversible. The financial drain may be unsupportable. The diarrhea associated with the pathologic process, or resulting from extensive resection, may make ordinary social contacts undesirable or not feasible for the patient. There is no discussion in any of the articles which includes reports of cases surgically treated that the writer has been able to find, including many which are not listed in this paper, which indicates how the principle of rehabilitation has been applied to the patients in the postoperative series. Not even the recent and otherwise complete monograph by Crohn (3) includes a discussion of this phase of management.

CONCLUSIONS

What then can be derived from this amorphous mass of material culled from the literature regarding the particular type of surgical management which should be applied to the particular case of regional enteritis?

First let us dispose of the question of simple exploration and/or appendectomy. In the case of acute regional ileitis, the diagnosis will seldom be made preoperatively; therefore, many cases will be explored who do not have obstructive symptoms. With a careful technique and the avoidance of drainage in the peritoneal cavity no harm appears to result from this procedure. If appendectomy is performed there is an immediate, though not very large, danger of establishment of a fistula. This is due to the finding that the principal, and usually sole, involvement of the cecum is represented by edema and lymphatic engorgement in the serosa, which may lead to break down at the suture line. The most experienced writers are now agreed that since histologic examination of such appendices reveals only edema that unless there is unmistakable evidence of acute appendicitis, that appendectomy in the acute stage of the disease offers nothing but a hazard. The great number of cases with previous appendectomies for the same or similar symptoms appearing in all series is a sufficient answer in justification of this viewpoint. Where suppuration and local peritonitis have already occurred a careful toilet of the area accompanied by the systemic administration of the appropriate antibiotics and without drainage of the peritoneal cavity is the procedure of choice.

With regard to the choice between ileo-transverse colostomy with and without transection of the ileum, there appears to be very little question that the latter group produce the greatest number of cases of persistence and recurrence of the disease of any of the operative procedures. The original fears that the excluded loop of ileum might become dangerously dilated (Holm, 32) have not been borne out by experience.

It appears likely that the indications for performing a one- or two-stage procedure if resection is contemplated depend principally on the patient's general condition. With proper timing and the judicious use of the presently available adjuvants to surgery the mortality for extirpation of the diseased bowel should be very low. There may be a disposition on the part of some to elect a waiting period following the first stage and to select only those with persistence of symptoms for the second stage procedure. In complicated cases, such as those with fistulas, the necessity for staging is obvious. The use of the Mikulicz procedure in resection seems to contradict the principles which are so generally agreed upon with regard to exploration: that is, that the establishment of direct communication between the skin and peritoneal cavity may lead to fistula formation. It does not seem logical to advocate wide resections of mesenteric nodes where other channels of lymphatic spread through the serosa of the large bowel are left intact.

Finally, the choice between resection and side-tracking alone cannot be decided on the basis of the figures that have been presented for all of the reasons given above. The experience is too diverse, the surgery too varied, the follow-up period in most instances too short, the duplication of cases too great, and the emphasis on rehabilitation as the final phase of the treatment almost totally lacking. It can probably be fairly stated that too many cases which have been subjected to resection have been adjudged failures due to the persistence of the one symptom of diarrhea. It is now a common experience for long segments of small and large bowel to be resected for other types of disease with diarrhea resulting. This can often be controlled by careful dietary and medical management.

Individualization of management must remain the rule in the treatment of diseases of uncertain etiology. Any attempt to standardize the treatment of regional enteritis on the basis of the incomplete information now available may only serve to halt progress toward the eventual solution of this problem.

SUMMARY

A review of the significant contributions to the literature on the surgical management of regional enteritis has been made.

Eight cases from the experience with this disease at the Meriden Hospital and from the author's experience have been presented from the standpoint of their surgical management and the results.

An analysis of the claims made for the greater efficacy of any particular surgical procedure in the treatment of this disease over any other does not show them to be fully justified by the results presented.

The burden of opinion is against appendectomy and/or drainage of the peritoneal cavity in acute regional enteritis.

The procedure yielding the poorest results appears to be ileocolostomy without transection of the ileum.

Sufficient emphasis has not been placed on the psychosomatic aspects of this disease and the necessity for mental, physical, social and economic rehabilitation of the patient following surgery.

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NON-PSYCHOGENIC FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT

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ALL TOO OFTEN the busy practitioner of medicine is inclined to apply a few select laboratory and roentgenologic studies to his patients presenting gastrointestinal complaints, and on finding no organic disease manifested tends to catalogue the patients as having a psychogenic disorder with gastroenterological manifestations. Certainly a respectable percentage of such patients have a purely psychogenic basis for their complaints, but the thorough diagnostician must never forget that a goodly number of these patients have functional disorders which are non-psychogenic in nature. In all fairness it should be stated that the dividing line between psychogenic and non-psychogenic functional disorders in certain given patients is rather indefinite. This is best exemplified by the modified motor function of the gastrointestinal tract during emotional disturbances. In other cases, the dividing line between organic and non-psychogenic functional disorders is equally indefinite. This paper is concerned primarily with the middle-zone or non-psychogenic disorders.

Perhaps it would be well to attempt to define a non-psychogenic functional gastrointestinal disorder. This is a condition in which a patient has gastrointestinal symptoms, and frequently gastrointestinal signs, due to impaired motor and/or secretory function and on whom tissue studies by the pathologist are negative for definite evidence of organic disease of the gastrointestinal tract. An appreciable percentage of these disorders represents gastrointestinal manifestations of organic disease elsewhere in the body.

Certain prolonged or excessively acute non-psychogenic functional disorders may result eventually in demonstrable organic disease in the gastrointestinal tract.

For the purpose of discussion these non-psychogenic functional disorders are divided into three groups: (1) Neurogenic, (2) Metabolic and (3) Miscellaneous.

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NEUROGENIC

Non-psychogenic functional disorders of the gastrointestinal tract may be secondary to a number of neurological diseases. Probably the most frequently recognized of these includes epilepsy, migraine and the abdominal manifestations of the tabetic crises. The general condition of epilepsy may have protean manifestations and the gastrointestinal tract may be the system with a predominance of symptoms (1, 2, 3, 4). The history is probably the most important factor in making the diagnosis of abdominal epilepsy. The

seizures tend to be sudden in onset and of variable duration. Pain may be the presenting complaint. A goodly percentage of these patients have electroencephalographic changes compatible with a convulsive disorder. Therapeutic response to anticonvulsants also aids in the confirmation of the diagnosis.

As has been stated so aptly by Dr. Alvarez (5), migraine equivalents are usually found in individuals with a migrainous temperament; is characterized by severe nausea, vomiting and prostration; but is not accompanied by pain, fever or abdominal bloating or rigidity. Many of these individuals have been subject to typical migraine in their earlier life.

A third neurogenic cause of gastrointestinal symptoms is the gastric crises of tabes dorsalis (6). This condition is manifested by recurrent episodes of severe abdominal pain accompanied by vomiting and having an abrupt onset and cessation. A single episode may last from a few hours to as long as two weeks. Some of these patients develop severe hematemesis. Almost invariably these patients have the usual signs and symptoms of tabes dorsalis in addition to their gastrointestinal manifestations, so that the diagnosis should be rarely missed if a careful history and physical examination are carried out.

METABOLIC

The second major group of the non-psychogenic functional gastrointestinal disorders is that associated with the metabolic diseases. By far the most commonly encountered member of this group is functional hypoglycemia (8, 9). In all fairness it should be pointed out that many workers consider this classification to be more psychogenic than non-psychogenic. Whatever its correct classification be, it is a frequently encountered condition when it is thought of and sought for. A careful history will usually suggest the condition to the thorough diagnostician. The symptoms of hypoglycemia almost never occur within one hour's time after eating. Blood sugar studies frequently may be misleading because of the individual's variation in the hypoglycemic threshold in susceptible persons. Perhaps the simplest test for functional hypoglycemia is the intravenous administration of a small dose of regular insulin to an individual in a fasting state. If this procedure reproduces his symptoms he most likely has functional hypoglycemia. It is well to remember, however, that the apparent functional hypoglycemia may be the result of organic disease elsewhere in the body. This is not an infrequent finding in chronic liver disease.

Diabetes mellitus (10) may produce symptoms which cause its inclusion into this group. The symptoms may vary from those of the suggested acute abdomen of diabetic acidosis to the vague gastrointestinal complaints of poorly controlled mild diabetes.

Addison's disease also must be mentioned in this group. The acute phase may attract attention to the gastrointestinal tract by its anorexia, nausea, vomiting and diarrhea. Even the chronic phase tends to be accompanied by vague gastrointestinal complaints.

Hypothyroidism may be accompanied by anorexia, constipation, abdominal distention, paralytic ileus, etc. (11). About 50 per cent of these patients tend to have associated organic disease in addition to that of the thyroid itself.

It is a well established fact that disturbed acid-base or electrolyte balance may cause gastrointestinal complaints. The commoner disorders in this category include acidosis, alkalosis, heat exhaustion, post surgical states, etc. Some of the above named metabolic diseases actually have their gastrointestinal manifestations on the basis of disturbed acid-base or electrolyte balance.

MISCELLANEOUS

The third major group of non-psychogenic functional gastrointestinal disorders is best classified as miscellaneous because of the large number of unrelated conditions catalogued under it. The first of these is gastrointestinal allergy. The symptomatic manifestations of this disease may vary greatly, depending upon which portion of the gastrointestinal tract is the "shock organ." Many of these patients have known allergy or have a positive family history of allergy. The onset of an acute episode is usually sudden and may even have a seasonal incidence. Many of these patients know of certain foods which they cannot tolerate. Unfortunately, skin tests tend to be of little value in the diagnosis of gastrointestinal allergy. Elimination diets are of importance both diagnostically and therapeutically (12). Special x-ray studies may be of value when the suspected agent is added to a barium study (13, 14).

Drugs, including local irritants, histamine, estrogens, cinchophen, heavy metals, the newer antibiotics, etc., may cause functional disturbances of the gastrointestinal tract; but at times, at least temporarily, the changes may be more organic than functional. Excesses of coffee and tobacco may result in functional disturbances. Improper eating habits and cathartic habituation may be followed by general gastrointestinal symptoms. Various chronic systemic diseases not discussed above may have a predominance of gastrointestinal symptoms whether they be due to general debility, reflex mechanism, edema, spasm, direct encroachment or disturbed acid-base or electrolyte balance.

SUMMARY

1. Some of the commoner non-psychogenic functional disorders of the gastrointestinal tract are briefly discussed.

2. As is true of diagnosis in general, these diseases must be thought of to be diagnosed.

3. Organic disease of the gastrointestinal tract should be sought for, even in patients presenting a seemingly pure psychogenic or non-psychogenic functional disorder.

4. A non-psychogenic functional disorder of the gastrointestinal tract may be a manifestation of organic disease elsewhere in the body.

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ABSTRACTS ON NUTRITION

FINCH, C. A., HEGSTED, M., KINNEY, T. D., THOMAS, E. D., RATH, C. E., HASKINS, D., FINCH, S., AND FLUHARTY, R. G.: *Iron Metabolism. The pathophysiology of iron storage.* Blood, V, 11:983-1008, Nov. 1950.

Storage iron is tissue iron which is available for hemoglobin synthesis when the need arises. This iron is stored in protein complex as ferritin and hemosiderin. Iron is transported by a globulin of the serum to and from the various tissues to satisfy their metabolism. Surplus iron carried by this iron-binding protein is deposited chiefly in the liver. Storage iron is relatively increased when the number of red blood cells is reduced — the exceptions being hemorrhagic and iron-deficiency anemias. Storage iron is absolutely increased following excessive iron absorption or parenteral iron administration. That iron in large amounts is toxic to tissues is suggested by the occurrence of fibrosis in organs most heavily laden with iron. Hemochromatosis is believed to be due to excessive absorption or parenteral administration of excess iron.

STAMLER, J., BOLENE, C., HARRIS, R., AND KATZ, L. N.: *Effect of choline and inositol on plasma and tissue lipids and on spontaneous and stilbestrol-induced atherosclerosis in the chick.* Circulation, II, 5, 722-725, Nov. 1950.

The lipotropic factors, choline and inositol, were found to be without effect on plasma and tissue lipid concentrations in either plain mash-fed or stilbestrol-treated birds. These factors failed to reduce either the incidence or severity of spontaneous or stilbestrol-induced atherosclerosis.

STAMLER, J., BOLENE, C., HARRIS, R. AND KATZ, L. N.: *Effect of choline and inositol on plasma and tissue lipids and atherosclerosis in the cholesterol-fed chick.* Circulation, II, 5, 714-721, Nov. 1950.

The ability of choline plus inositol to protect against cholesterol-induced atherosclerosis was studied in chicks fed one-fourth per cent, one-half per cent, and two per cent cholesterol. The lipotropic factors tended to aggravate hypercholesterolemia, although they exerted a partial, incompiete lipotropic effect against cholesterol-induced hepatic lipidosis and cholesterosis. The aorta was most frequently and most severely affected by atherosclerosis in those groups receiving the lipotropic agents.

STAMLER, J., AND KATZ, L. N.: *Production of experimental cholesterol-induced atherosclerosis in chicks with minimal hypercholesterolemia and organ lipidosis.* Circulation, II, 5, 705-713, Nov. 1950.

Feeding chicks a mash enriched with 0.25 per cent cholesterol plus 5 per cent cotton seed oil induced a minimal sustained hypercholesterolemia and hepatic lipidosis. After 35 weeks on this diet a high incidence of gross cholesterol-induced atherosclerosis of the aorta was present, being particularly prominent in the thoracic aorta. This type of atherosclerosis aparently resembles the human disease, and the experiment suggests that exogenous cholesterol plays a part in both.

GERTLER, M. M., GARN, S. M., AND WHITE, P. D.: *Diet, serum cholesterol and coronary artery disease.* Circulation, II, 5, 696-704, Nov. 1950.

The authors believe there is no advantage to be gained from imposing a low cholesterol diet on patients with coronary artery disease. A dietary survey indicated that persons having had myocardial infarction prior to the age of 40 years had not eaten as much cholesterol per week as the normal controls, nor was there any definite relation between the amount of cholesterol ingested and the level of cholesterol in the serum.

GIRDWOOD, R. H.: *The intestinal content in pernicious anemia of factors for the growth of streptococcus faecalis and lactobacillus Leichmannii.* Blood, V, 11, 1009-1016, Nov. 1950.

The gastric juice and secretions of the small intestine in three cases of untreated pernicious anemia and in two control patients during a period of fasting contained only very small amounts of folic acid or of factors for the growth of *L. leichmannii*, which include vitamin B_{12}. There was no evidence of a consistent increase or decrease of these factors along the intestine. Both folic acid and vitamin B_{12} appear to be synthesized in relatively large amounts in the large bowel. In a patient with pernicious anemia the daily output in the stools may be about 5 mcgm. of vitamin B_{12} and 0.5 mg. folic acid. Similar quantities may be present in patients not suffering from this disorder.

DEAN, H. T., ARNOLD, F. A., JR., JAY, P., AND KNUTSON, J. W.: *Studies on mass control of dental caries through fluoridation of the public water supply.* Pub. Health Rep., 65, 43, 1403-1408, Oct. 27, 1950.

Fluoridation of the Grand Rapids public water supply began in January 1945. Analysis of the 1949 dental examinations at Grand Rapids shows a reduced amount of dental caries experience when compared with the pre-fluoridation rates of 1944-45. The findings indicate that the reduction is most pronounced in the younger age groups whose dentition was largely calcified following the addition of one part per million of fluoride to the previously fluoride-free public water supply. Sufficient time has not elapsed to evaluate water fluoridation in the older age groups.

WEINSTEIN, J. J.: *Nutritional management of patients with colon surgery.* A. J. Proctology, 1, 3, 110-122, Sept. 1950.

Success in surgery of the colon depends partly upon taking care of the nutritional, fluid and electrolyte needs of the patient before, during and following operation. Diseases of the colon frequently occur in the chronically ill in whom anemia, hypoproteinemia and general nutritional inadequacy are present. The author outlines in detail a pre-operative regime which has been successful in his hands. Briefly expressed, it is a system of making good protein lack and of

establishing positive nitrogen balance, and involves blood transfusion and special feeding schedules.

SCHNEIDER, R. W.: *The use of anti-lewisite (BAL) in the treatment of diabetic neuropathy.* Cleveland Clin. Quart., 17, 4, 197-208, Oct. 1950.

Twenty-two patients with diabetic neuropathy were treated with BAL. Of these, 12 were relieved of pain and also most of the distress attending the neuritis. Eight of them experienced an intensification of pain following almost every injection and have remained free of recurrences. Four, who showed no intensification of pain, tended toward relapse. Ten patients experienced no benefit. Beneficial effects of BAL are probably due to some influence on the enzyme systems of the neurones. Comparatively small doses were used. While BAL usually is used in poisoning with heavy metals, Furmanski years ago showed that some cases of peripheral neuritis not associated with metal poisoning were helped by its use. In diabetes there is no evidence that poisoning with metals occurs. The results with BAL are definitely encouraging.

JOHN, H. T.: *Statistical study of 6,000 cases of diabetes.* Ann. Int. Med., 33, 4, 925-940, Oct. 1950.

The national incidence of diabetes is between one and two per cent of the population, being low in the first three decades and heaviest from the fifth decade on. The renal threshold for sugar varies from 50 to 600 mg. per cent of blood sugar. Sixty-two per cent of the males and 69 per cent of the females in this series had been at some time 11 per cent overweight. Weight reduction improves carbohydrate tolerance but does not cure diabetes. Infection plays a role in precipitating diabetes. The most frequent cause of death was cardiorenal disease; next came diabetic coma; then post-operative deaths, including operations for gangrene; then pneumonia. In the diagnosis of diabetes, the length of time the blood sugar remains elevated following a meal is of most importance. If hyperglycemia is present 2½ hours after a meal, the case is considered as one having diabetes.

KAMDHORN SUVARNAKICH: *The Thai Diet.* Nutrition Reviews, 8, 10, 289-291, Oct. 1950.

The author, a practitioner in Bangkok with special interest in nutrition, says his experience in Thailand has led him to believe that a diet high in protein and fat may contribute to the causation of some metabolic diseases. Thus diabetes and hypertension occur among the well-to-do urban populations who employ such diets, whereas these two diseases are comparatively rare among farmers who subsist mainly on rice diets high in carbohydrate, but low in protein and fat. Malnutrition, when it occurs in Thailand, is due to the traditional belief that rice is the only food needed by the human body. Such items as pork, fish, lard, eggs, vegetables, peppers and spices are used mainly in preparing rice dishes. Vegetables and fruits rank next to rice in quantities consumed and they provide vitamins A and C and some of the B-complex. Beri-beri does occur in Thailand but there is no rickets and no cases of clear-cut clinical malnutrition. Anemia and leanness often are due to malaria and other tropical diseases. The average diet contains 3300 calories, 81 per cent carbohydrate, 10 per cent fat and 9 per cent protein. The daily protein intake is 76 grams, 40 grams of which comes from rice. The average blood pressure among a hundred soldiers was 106/67 mm. Hg. These soldiers were active, lean and obviously in good health in spite of the fact that only half of their protein came from animal sources. No doubt this illustrates the supplementary action of the two types of protein. Obesity is not a problem in Thailand because the people do not overeat. The question of longevity in relation to rice diet cannot be answered. The shorter life expectancy in Thailand is complicated by problems of personal hygiene, sanitation, medical care and tropical diseases.

THOSTESON, G. C.: *Diabetic detection is important.* Harper Hosp. Bull., 8, 5, 131-133, 1950.

The urgent importance of diabetes detection from the standpoint of the patient is emphasized. In such detection it is fallacious to rely on the morning urine specimen as a sole guide. Again, not too much significance is to be attached to a normal fasting blood sugar. A blood sample taken 1½ hours after a meal high in carbohydrate is really significant. A level of 170 mg. at this time is strongly suggestive of diabetes. A family history of the disease, adiposity, and the chance discovery of glycosuria should always call for a careful examination of urine and blood.

ENNOS, E. H.: *Some aspects of fat metabolism.* Med. J. Australia, 432-434, Sept. 16, 1950.

After an examination of what is known regarding the nature of fat oxidation by the liver, the author propounds the theory (which as yet has insufficient evidence to support it) that the accumulation of liver fat which occurs after the administration of many hepatoxic substances is not, in itself, a pathological process but one which merely reflects the demand for energy needed for the repair of the "biochemical lesion." Until the biochemist has succeeded in explaining the biochemical lesion in cases of intoxication, we cannot expect to be able to reverse it before it has gone too far.

LOWE, T. E.: *A study of sodium and water balances in congestive cardiac failure.* Med. J. Australia, 497-500, Sept. 13, 1950.

The author studied congestive cardiac failure by recording the water and sodium balances during treatment of patients on a regime consisting of bed rest, restriction of sodium intake, free fluid intake and, in some cases, the exhibition of mercurial diuretics. These studies revealed two types of subjects of cardiac failure: first, those that respond to bed rest, sodium restriction and free fluid intake; second, those that fail to respond to this therapy until mercurial diuretics are given. It was noted that patients in the second group excreted excess amounts of pituitary antidiuretic hormone in the urine.

EDITORIALS

DIETS LOW IN ANIMAL PROTEIN

CURRENT NUTRITIONAL THOUGHT favors the use of diets high in animal protein in the treatment of many diseases and for the maintenance of health. The complete biological proteins contained in meat — particularly liver — and in eggs and milk possess specific value in some diseases of the liver, in certain macrocytic anemias and in establishing and maintaining positive nitrogen balances in a number of other diseases. Seyle and others have emphasized, however, in connection with the study of the so-called "diseases of adaptation," that a high protein diet plays some part, under conditions of stress, in activating ACTH and therefore in causing the subsequent clinical catastrophes which depend upon the release of mineralocorticosteroids from the adrenal glands. (The general failure of low protein diets to benefit cases of established hypertension does not deny the role of high protein diets in their causation, at least in certain instances.)

Recently, Suvarnakich (1), a medical practitioner in Bangkok, who has devoted special attention to nutrition in Thailand, has pointed out that some metabolic diseases, especially diabetes and hypertension, are common among well-to-do urban populations in

Thailand who indulge in high protein diets with their inevitable high fat content. He noted, on the other hand, that these diseases were rare among the farmers who subsist mainly on rice diets, high in carbohydrate and low in protein and fat. He comments on the splendid physical condition of 100 Thailand soldiers who were maintained on 3300 calorie diets with only seven per cent of protein. Of the total of 76 gm. protein daily, only 36 gm. were derived from animal sources. The average blood pressure of this group was 106/67 and there was no evidence among the soldiers of malnutrition.

This report from Thailand at least challenges the scientific criteria in our possession with respect to the essentiality of animal protein for the maintenance of health. The problem is not academic but practical, because in many regions of the globe people are forced to subsist on diets whose protein is obtained almost exclusively from cereal sources. Obviously such diets could be improved by the addition even of very small amounts of animal protein to the customary meals in order to take advantage of the supplementary action of the two types of protein.

Suvarnakich's report also raises the question as to whether a diet low in animal protein may or may not possess some advantages in normal persons over diets containing excessive amounts of animal protein and fat. While we know that high animal protein diets provide greater physical stamina, it is quite possible that low animal protein diets may provide a partial safeguard against illness, particularly to persons living under the tensions of modern civilization.

The question of longevity in relation to diets low in animal protein cannot be answered in terms of human experience because those present populations who subsist on such regimes are subjected to shorter life expectancies by tropical and parasitic diseases, poor sanitation and medical care and by problems in personal hygiene. For us, living under excellent hygienic conditions and with a relative abundance of animal protein food at our disposal, the question as to how much meat to eat and how much to advise others to eat, may be more important than is usually considered. Until the point has been further clarified, it is easy enough to assume that under conditions of great personal stress it may be wise to restrict the amount of meat consumed. Such a diet cannot reverse established metabolic disease, but in some instances, it may prevent the beginnings of the steroid process of "adaptation," which exerts such lethal effects.

(1) SUVARNAKICH, K.: *The Thai Diet.* Nutrition Reviews, 8, 10, 289-291, Oct. 1950.

B. P. BABKIN

WE RECORD WITH REGRET the death of B. P. Babkin, M.D., D.Sc., D.L.B., Research Professor of Physiology at McGill University and, for many years, an active member of the Editorial Council of this Journal. His death occurred on the train on May 2nd while he was returning to Montreal from a medical meeting in Atlantic City. He was born in Russia but expelled in 1922 because he opposed the Soviet philosophy. For two years he worked with Starling in London, coming then to Canada, working first at Dalhousie University and finally at McGill. He was best known for his work on the digestive tract, which is summarized in his monumental book, *Secretory Mechanisms of the Digestive Glands.* He is universally regarded as the greatest authority of the twentieth century on the physiology of the digestive glands. Pavlov offered him his own post at the Military Medical Academy in Leningrad but he declined it, because he felt that in Canada science would remain unhampered by government and irrational ideologies. At the time of his death his attention was focused on the functions of the cortex in the regulation of digestive functions. He was a serious student of music and also a composer. His relationships with this Journal were characterized by directness, frankness and helpfulness. A great man has passed and his place will not soon be filled.

BOOK REVIEWS

PAINLESS RECTAL SURGERY. Alfred J. Cantor, B.A., M.D., F.I.A.P. 180 pages, Hippocrates Press, New York 1951, $4.50.

Hippocrates Press presents with pride the first of a series of "waiting room books" designed to instruct the patient in the meaning of his symptoms, and to impress upon him the need for consulting first his family doctor. The book deals with ambulant rectal surgery in a systematic and revealing way and is written in popular English, and very attractively. Most, if not all, the surgical conditions of the rectum are covered adequately. Brief marginal summaries in red type increase the ease of reading. Obviously Dr. Cantor has had an educational objective in mind, namely to indicate the advantages and comfort of ambulatory proctology. The book is one which, because of the author's erudition and good judgment, may safely be recommended for those patients who wish to know more about the meaning of their illnesses. We recommend it without reservation.

THE EXTERNAL SECRETION OF THE PANCREAS. J. Earl Thomas, M.D., 160 pages, Charles C. Thomas, Springfield, Illinois, Dec. 10, 1950, $3.50.

A well-documented and clearly illustrated monograph on the various aspects of pancreatic anatomy and physiology, written from the scientific standpoint, is presented for physicians as well as students and teachers. Secretin is fully described. Judgment is reserved with respect to the status of pancreozymin. The chapters on the functional innervation of the pancreas and the mechanism of pancreatic secretion are particularly valuable and informative. Dr. Thomas is to be congratulated on having produced a succinct but adequate description of what is known about the pancreas, and most physicians will desire to study the book in detail.

PHARMACOLOGICAL BASIS OF PENICILLIN THERAPY. Karl H. Beyer, Ph.D., M.D., F.A.C.P., 215 pages. Charles C. Thomas, Springfield, Illinois, 1950, $4.50.

This is the first time that the broad field of penicillin pharmacology has been completely reviewed. The action of penicillin, its chemical, physical and anti-bacterial properties, its distribution in the body and the methods of its elimination are fully dealt with. There is an added section on Benemid, known to enhance greatly the value of penicillin therapy. Beyer makes the interesting observation that although the body possesses a "physical abhorrence of penicillin," resisting its entry and facilitating its exit, this agent has actually revolutionized the practice of medicine. No active physician should be without this valuable treatise.

DIANETICS. L. Ron Hubbard, 452 pages. Hermitage House, New York, 1950, $4.00.

Because a considerable mass of non-medical people have been puzzled by this book, and some of them seek the opinion of physicians with respect to its value, it might be an advantage if the physician could have it appraised without being forced to read it. This review, made for that purpose, takes the attitude that Hubbard has not produced any scientific proof to support his theories, and consequently "dianetics" is unacceptable as a means of psychotherapy.

He replaces the unconscious mind of psychoanalysis by a sub-mind ("reactive mind") which is always conscious, even when the individual is unconscious. The impressions made upon this "reactive mind" by environment and experience are called *engrams*. Though dormant, engrams may be reactivated by a repetition, during consciousness, of the experience originally producing them. This reactivation gives the engram "command power" over the individual, blocking all attempts of the conscious mind to disobey such command. The upshot is that everyone's power to think is interfered with by such engram activity (pain records) so that few persons possess more than 10 per cent of their "potential awareness."

This sad state of affairs, however, ought not to give us the slightest concern because dianetic therapy deletes all the pain from a life-time, causing all aberrations and psychosomatic illness to vanish. How? In reverie, with a professional therapist nearby, the patient returns and re-lives the experience of the engrams. This simple process removes the pain and blocking effect of the engrams which are now "filed" as useful memory. The individual is thus "released" and becomes a "clear," or normal.

That the dynamic principle of existence is survival will be easily accepted by most biologists. That the fundamental and basic nature of man is *good* (which Hubbard states as an irrefutable axiom) is by no means easy to prove or deny. That even the most severe psychological blocking readily yields to a process resembling meditation is quite out of line with the experience of most, if not all, psychologists.

Physicians would be wise to advise patients enquiring about "dianetics" to leave the subject alone. Introspective activities, even when assisted by a lay or "professional" therapist, are harmful to many individuals. The book is written in a vein of such optimistic euphoria as to cast suspicion on its fundamental soundness. In all psychoanalytic experience, if one thing is agreed upon, it is this — that the blocked complex seldom is relieved easily.

GENERAL ABSTRACTS

WOLF, S.: *Summary of evidence relating life situation and emotional response to peptic ulcer.* Ann. Int. Med., 31, 4, 637-649.

In many cases peptic ulcer probably results from disturbed gastric function in response to stresses in the life situation. Personal conflict can induce gastric hyperfunction and ulcer-type pain, and these seem to be mediated through the vagus stimulation. A discussion of significant personal problems with persons having peptic ulcer may produce hyperacidity, hypermotility and pain.

DORET, J. P.: *Critical study of the gastrographic diagnosis of duodenal ulcer.* Helv. Med. Acta, 16, 3/4, 240-243, Sept. 1949.

Drinking 40 to 100 cc. of cold water at 15°C inhibits for some time the muscular contractions of the stomach in healthy persons. According to Kay, this reflex does not occur in patients with duodenal ulcer, but recurs when they are healed. Doret tried out the Kay test in 25 patients and was unable to confirm the conclusions of the English author. He did not find the phenomenon pathognomonic of duodenal ulcer for it occurred also in most patients with ulcer irrespective of its site and also in pseudo-ulcer and nearly always in hyperchlorhydria from whatever cause. Doret regards the phenomenon as an indication of a nervous disorder and as an element in the pathogenesis of ulcer.

M. Demole, Geneva.

MERKE, F.: *Concerning cancerized ulcer.* Helv. Clin. Acta, 16, 2, 105.

Four hundred fifty gastrectomies were performed for peptic ulcer (257 gastric and 203 duodenal) and microscopic examination revealed malignant degeneration in nine per cent of gastric ulcers, and as high as 14 per cent in the case of deep callous ulcers. In the duodenum a cancerized ulcer was found only once. There are no definite signs to inform us when a benign ulcer is about to become malignant. At times an unexpected aggravation of symptoms occurs, but usually the ulcer history dates back so far that such a warning is not very clear. After publishing the records of 22 patients with malignant degeneration of ulcers, Merke concludes that gastric ulcer should be removed early to avoid this complication.

M. Demole, Geneva.

PEARSON, C. C., AND BROWN, P. V.: *The emetic crisis of peptic ulcer.* Bull. Mason Clin., Sept. 49, 3, 3, 15-19.

The authors have recently seen five cases (two of which are described) in which the presenting symptom was marked vomiting and in which duodenal ulcer was demonstrated. Apparently this emetic crisis of ulcer has been a neglected subject, since one usually does not think of vomiting in ulcer except with pyloric block — which was not present in their cases. A long ulcer history should focus the attention of the physician on this possibility but of course x-ray demonstration of the lesion is final. One of the cases described could have been regarded as one of anorexia nervosa, and the other as nicotinism or alcoholism. Even virus "x" might have been considered. Retention was negligible. Medical treatment is indicated. One of the patients had a burning sensation in the upper abdomen. Pain is not mentioned as a definite accompaniment of the vomiting.

DE VAN, W. T.: *The preoperative use of streptomycin in gastrointestinal surgery.* Bull. U. S. Army Med. Dept., Sept. 1949, 9, 10, 818-828.

Forty patients on whom gastrointestinal operations were performed were prepared for operation by the administration of 1 gm. streptomycin by mouth every six hours for five days. No ill effects were noted apart from a mild diarrhea in half the cases. In about 40 per cent of the cases, the stool was sterile in 48 hours for aerobic and anaerobic organisms, and about 48 per cent sterile stools occurred in 72 hours. The prothrombin levels fell after repeated doses of the drug, but rarely to alarmingly low levels. All patients receiving streptomycin per os should be given moderate doses of vitamin K to counteract the concurrent rise in prothrombin time.

BERMAN, J. K., AND LEE, W. V.: *Traumatic injuries to the liver and spleen.* J. Indiana State Med. Assn., 43, 10, Oct. 1950, 1001-1004.

A study of the leukocyte counts in early phases of abdominal trauma indicates that they constitute an aid in the diagnosis of injury to the liver and spleen. (Such counts are reliable only during the first few hours following injury, before replacement of fluids.) White blood cell counts are higher in ruptured wounds than in perforating or penetrating wounds, and they are also accompanied by a greater fall in hemoglobin.

KARN, H.: *The history of acute appendicitis.* New Zealand M. J., XLIX, 272, Aug. 1950, 400-411.

Prior to 1800 only three cases of appendicitis had been reported in Europe and America. Between 1800 and 1860, 126 cases were reported. The older names — typhilitis, perityphilitis — were replaced by appendicitis after Reginald Fitz in 1886 read a paper on it at the first meeting of the Association of American Physicians in Boston. The public became

widely acquainted with the disease because of the publicity attending the attack of appendicitis suffered by King Edward VII just prior to his coronation. Sir Frederick Treves successfully performed the operation, and the coronation ceremonies had to be delayed.

PARKINSON, D., DOCHERTY, M. B., AND CRAIG, W. M.: *Retroperitoneal ganglioneuroma.* Proc. Staff Meet. Mayo Clin., 1949, 24, 22, 549-554.

The case of a 20 year old female is described who presented a smooth, rounded, firm, slightly tender mass, eight cms. in diameter, in the right mid-abdomen, which could be clinically differentiated from the right kidney. It proved to be a retroperitoneal ganglioneuroma and was successfully removed through a flank incision. The right sympathetic trunk was continuous through the tumor, which produced some compression of the right ureter and calyx. A postoperative sweating test demonstrated complete anhydrosis from the first lumbar segment downward. The patient had complained of a dull aching pain in the lower right quadrant, with occasional extension to the upper part of the thigh. There was a genito-femoral nerve analgesia in this same region, so that her pain obviously was due to pressure on this nerve. Most of these tumors which arise from the primitive neuro-ectoderm are rather benign but the finding of neuroblastic elements in them signifies malignancy.

LATNER, A. L.: *Regime for treatment of severe and acute liver disease.* Brit. Med. J., Sept. 30, 1950, 748-751.

Only one out of five cases of severe liver damage died under Latner's care, and the others made remarkably fast and permanent recoveries. No doubt these remarkable results were due to Latner's polytherapy. Two types of infusion were used. The first consisted of a pint of 10 per cent dextrose plus 50 mgm. of thiamine hydrochloride, 150 mgm. of nicotinamide, 50 mgm. of riboflavin and 0.5 gm. of potassium chloride. This infusion was given intravenously three times in the 24 hours. The second infusion consisted of blood plasma to which the vitamins alone have been added in the same concentration as in the first infusion. This second infusion is given once a day. Three hundred mg. of tocopherol are given intramuscularly in 24 hours in three divided doses. Penicillin and/or streptomycin are used for associated infection. Three of the patients developed macrocytic anemias with normoblastic marrows, the anemias responding to folic acid and blood transfusion. "The intravenous liver regime" of Latner should be given a wider trial in cases coming under the classification of acute yellow atrophy of the liver, with amino-aciduria as detected by paper chromatography.

BARCLAY, S.: *Operative relief of recurrent pancreatitis.* New Zealand Med. J., XLIX, August 1950, 419-423.

Choledocho-jejunostomy utilizing a jejunal side limb, is advocated as an effective treatment of recurrent pancreatitis. Cholecystojejunostomy, with preferably occlusion of the common bile duct, is an alternative. The advantages claimed over other forms of treatment of recurrent pancreatitis are, (a) Total diversion of bile from the region of the pancreatic duct should eliminate the possibility of further attacks whether pancreatic pain is due to inflammation of the gland from bile reflex, biliary infection, or hypertension in the biliary-pancreatic system. (b) Conservation of pancreatic function. (c) Absence of undesirable sequelae. There is no evidence whether or not pancreatic calculi *per se* produce pain. The effect of the operation in such cases is unpredictable but should be tried as an alternative to splanchnicectomy or pancreatectomy. Accepting the belief in a common termination of biliary and pancreatic ducts and excluding cases of total ampullary occlusion, there is no evidence that dysfunction of the terminal sphincter apparatus can produce pain in the absence of bile.

BAKER, J. W., AND HAWLEY, J. H.: *Surgical injury to the common bile duct: advantages of immediate repair: a case report.* Bull. Mason Clin., IV, III, Sept. 1950, 80-86.

A common duct from which 1.5 inches had been accidentally excised was surgically cured by a second operation in which, by mobilizing the pancreas, the two cut ends were brought together and sutured over a catheter which, brought through the duodenal and abdominal walls, was later withdrawn. The authors stress the importance of early re-operation in all cases of surgical injury to the common duct.

DOYLE, C. R.: *Surgical management of gastrointestinal conditions of the newborn.* Miss. Valley M. J., 72, 2, 45-47.

The author devotes himself to a discussion of congenital hypertrophic pyloric stenosis, and in a general way to the various atresias. In feeling for a tumor in pyloric stenosis, he suggests that if the patient be overfed sufficiently to produce regurgitation, the resultant flaccidity of the abdomen facilitates accurate palpation. X-ray study following a barium meal is seldom conclusive but may be confirmatory.

KESSLER, A. D., AND SCOTT, R. B.: *Atypical pyloric stenosis.* Arch. Pediat., 67, 2, 78-81.

Two negro infants are described in each of whom vomiting began on the first day of life, due, in both cases, to congenital hypertrophic pyloric stenosis. Ordinarily, symptoms usually begin about the fifth or sixth week of life. The condition itself is rare in the negro. The authors point out that in cases where x-ray studies are employed, one should use a thin barium mixture to avoid producing obstruction. They also note that, in the first two weeks of life, the normal emptying time of the stomach may be as long as eight hours. Of course the use of x-ray is not necessary to making the diagnosis, but is merely confirmatory.

SCHAFF, B., AND BORNSTEIN, S.: *Appendicitis during pneumoperitoneum treatment.* Am. Rev. Tuberculosis, 61, 3, 353-354.

The authors found that patients receiving pneumoperitoneum developed appendicitis five times more frequently than the remainder of the hospital population. The explanation for this increased incidence of acute appendicitis in pneumoperitoneum cases is not at all clear. The benefits derived from pneumoperitoneum in the treatment of pulmonary tuberculosis far outweigh the dangers from a slightly increased occurrence of appendicitis.

FLOYD, W. R.: *Thrombosis of the portal vein.* Southern Med. & Surg., 112, 2, 37-38.

Floyd presents two cases of idiopathic thrombosis of the portal vein, neither of which was diagnosed clinically. In one, with treatment by anticoagulants, recovery occurred from the thrombosis by recanalization of the portal vein, and he probably would not have died except for a gastric ulcer. Floyd believes that in early cases, or in cases in which operation reveals no nonviable bowel, resection is contraindicated and anti-coagulant therapy is the treatment of choice.

ADAMS, F. M.: *Gastrointestinal manifestations of myocardial infarction.* J. Arkansas Med. Soc., XLVI, 10, 171-173.

Adams presents five cases in four of which there were no chest symptoms associated with myocardial infarction, but in which all the symptoms were apparently related to the gastrointestinal tract and consisted of epigastric distress, nausea and vomiting. In each case the cardiogram was the essential finding contributing to the correct diagnosis. He quotes Katz to the effect that many persons have myocardial infarction without any symptoms, and survive the attack without any medical care.

FRIED, C. T., AND GRAND, M. J. H.: *Hypervitaminosis A.* Am. J. Dis. Child., 79, 3, 475-486.

The authors describe two cases of hypervitaminosis A. The disease is due to prolonged, excessive intake of vitamin A and a derangement of vitamin A metabolism. The clinical manifestations are anorexia, weight loss, extreme irritability, low grade fever, pruriginous rash, sparseness of hair, enlargement of the liver and exquisite pain on pressure over the long bones. Periosteal proliferation in the long bones is shown on x-ray. All reported cases have shown hepatomegaly. The highest blood serum levels ever reported for vitamin A are recorded. These cases gradually recover on removal of vitamin A from the diet.

FRANCO, V. B.: *Total gastrectomy.* Revista Brasil. d. Gastroent., I, p. 7, 1949.

A dietary and general regime is outlined for total gastrectomy, of which three cases are presented. One of them, 18 months following operation, has developed difficulty swallowing, and x-ray studies have indicated a tumor growth at the distal end of the esophagus. A jejunostomy has been done and it is planned to do a transthoracic esophagectomy.
— Author's summary.

RIBEIRO, E. B.: *Succinyl sulfathiazole in the preoperative treatment for intestinal surgery.* Revista Brasil. d. Gastroent., 1949, I, p. 180.

This is a review of medical attempts since 1886 to attain intestinal sterility. The discovery of succinyl sulfathiazole (sulfasuxidine) and of ftalil sulfathiazole (sulfatalidine), introduced into therapeutics by Poth and Knotts in 1941 and by Poth and Ross in 1943, is hailed as a notable landmark in gastrointestinal surgery. The review covers the experimental work on the effects of sulfonamides on the intestinal flora. Some of the author's cases are cited to show the excellent results of the preoperative use of sulfasuxidine.
— Author's summary.

VALADARES, C. D. P.: *Psychological assistance in colostomy cases.* Revista Brasil. d. Gastroent., 1949, I, p. 156.

The prospect of an unavoidable abdominal colostomy raises serious problems in the mind of the patient. Fear, ignorance, and vanity are important elements, and the psychologist, with little to go on, must fall back on the vital self-preservative instincts of the individual. The author uses strong suasion to obtain the patient's rational acceptance of the operation and, by simple arguments, he is shown the need of social assistance after he leaves the hospital. A series of methods to be used in preoperative treatment, adapted to the economic status of the patient, is presented.
— Author's summary.

TORDOIR, B. M.: *External anorectal prolapse in children during the war years.* Am. J. Dis. Child., 1949, 78, 5, 671-676.

During the war years in the Netherlands, the author treated surgically 52 cases of anorectal prolapse in children. The condition resulted largely from the diarrhea of starvation and the wasting of the ischio-rectal fat deposits. In 41 of the cases, he used the ring method of Thiersch and in 11 he used injections of quinine and urea hydrochloride. The ring method frequently caused suppuration and this resulted in a firm band of adhesions with some rectal obstruction. The injection method was preferred by the author, although there were no recurrences in any of the 52 cases.

WALTERS, W., AND PHILLIPS, S. K.: *Physiological aspects of repaired stricture of the extrahepatic bile ducts: report of 165 cases.* Proc. Staff Meet. Mayo Clin., Jan. 5, 1949, Vol. 24, No. 1, 12-16.

Nearly all strictures of the bile ducts are the result of injury at operation, and safe biliary surgery requires excellent exposure and lighting and complete familiarity with variations in the anatomy of the biliary tract and the hepatic artery and its branches. Any injury inflicted should be repaired at once. Strictures are not hopeless, though serious, and require accurate surgery before extensive infectious damage to the liver has occurred. Usually enough of the duct can be found above the stricture to enable the performance of a direct anastomosis between it and an opening made in the duodenum. Present day methods of prevention of bleeding and control of infection along with accurate anastomoses have produced a low mortality rate of 2.3 per cent in the last 86 operations performed by Dr. Walters.

GILD, A.: *Surgical treatment of cardiospasm: cardio-esophageal myotomy.* Med. J. Australia, Dec. 4, 1948, 658-661.

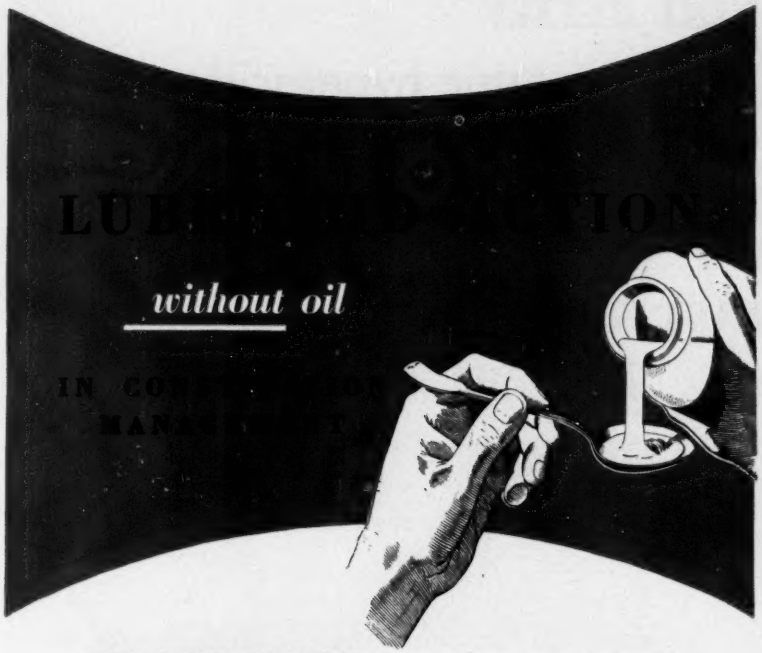
The author reviews the difficulties, dangers and advantages of internal dilatation by *per oral* methods of cardiospasm. He describes a method employing muscle cutting which in his hands and that of others has proved successful. A long left subcostal incision is made and, after dividing the left triangular ligament of the liver, the left lobe is pushed to the right, giving excellent exposure of the esophagus. The entire muscular coats of the esophagus and stomach are divided, without injury to the mucosa or to the left vagus nerve by an incision 8 cms. long, half of it on the esophagus and half on the stomach. The ligament of the liver is *not* sewn together again. Pre-operative and post-operative care is described.

BOYLES, J. M.: *Congenital diaphragmatic hernia on the right side.* Northwest Med., May 1949, Vol. 48, No. 5, 324-326.

Congenital diaphragmatic hernias on the right side are somewhat rare and the author describes the successful surgical treatment of such a case. The earlier the diagnosis and surgery, the better the results are likely to be. When a newborn babe has vomiting, rapid pulse, difficult breathing and cyanosis, the condition should be suspected. Diagnosis can easily be made with the aid of the x-ray.

BLACK, B. M.: *Recent advances in surgery of the colon.* Journal-Lancet, Aug. 1949, Vol. 69, No. 8, 275-278.

Chemotherapy is responsible for greatly decreased operative risk and has permitted marked changes in colonic surgery. For lesions of the right portion of the colon, one-stage resection with ileocolostomy is now standard procedure and carries about a three per cent mortality. For lesions in the balance of the colon, segmental resection with primary intraperitoneal anastomosis, usually without a proximal colonic stoma, is now used routinely. Exteriorization procedures may be required when obstruction, inflammation or obesity render end-to-end anastomosis technically unsatisfactory. Lesions in or near the rectum usually require a proximal colonic stoma. For lesions of the mid-rectum, single stage combined abdominoperineal resection is the operation of choice, although the hospital mortality rate of a procedure of this magnitude remains at five percent.



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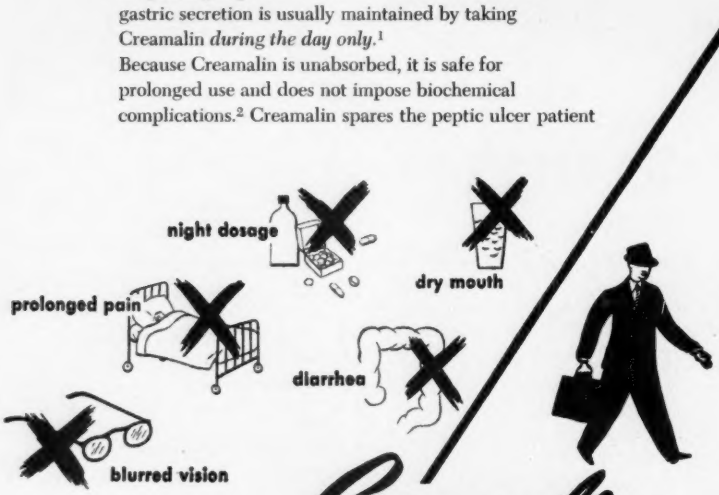

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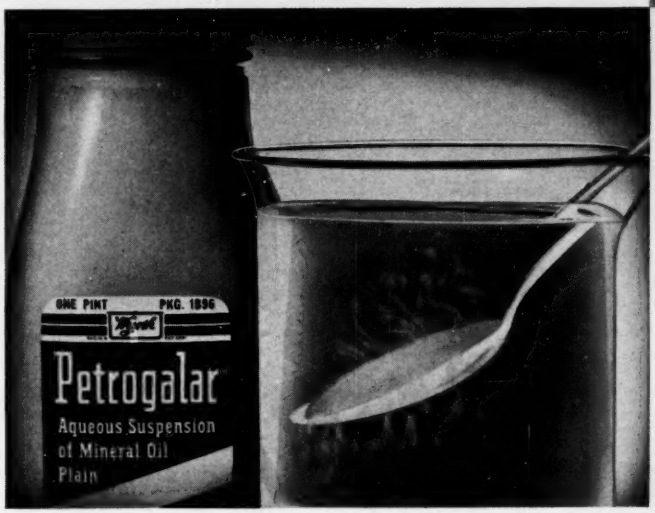

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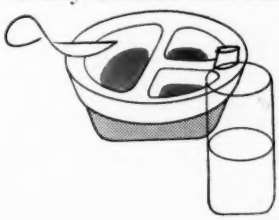

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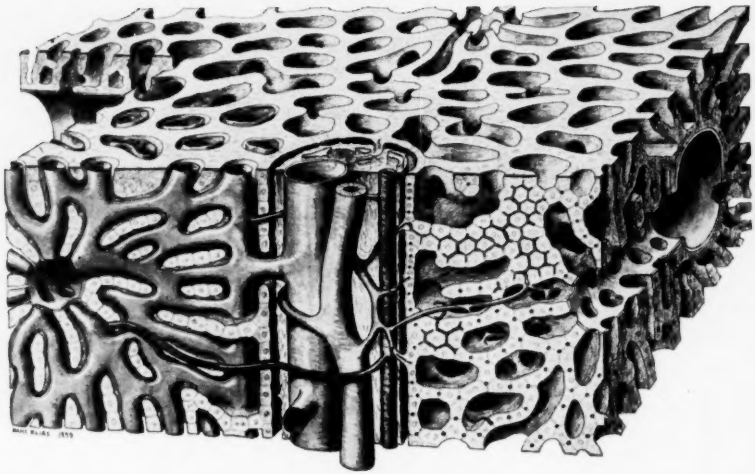

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